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REVIEW

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Are there links between Alzheimer's disease and ADHD? The efficacy of acetylcholinesterase inhibitors and NMDA receptor antagonists in controlling ADHD symptoms: a systematic review

Ramin Abdi Dezfouli[1*], Sara Akbariforoud[2] and Ensieh Esmaeilidezfouli[3]

Abstract

Background To assess the effectiveness, safety, and tolerability of anti-Alzheimer agents (memantine, galantamine, rivastigmine, and donepezil) in controlling ADHD symptoms in children, adolescents, and adults.

Methods Following the PRISMA guideline, clinical trials assessing the potency of anti-Alzheimer medications in managing ADHD symptoms were imported from PubMed, Web of Science, and Scopus (until February 2023). Screening stages were conducted by two independent researchers. Two independent researchers also extracted data from clinical trials reporting the outcomes as the reduction in scores of ADHD questionnaires. The risk of bias within the included studies was assessed using the Cochrane Collaboration tool, while the certainty of outcomes was evaluated based on the GRADE criteria.

Results Of the initial 1597 studies, 11 studies were included. No studies were available for rivastigmine, and only a single study was conducted for galantamine. The results of the other two medications had a slight inconsistency. While both memantine and donepezil were reported to be effective in several studies, they were reported to be ineffective in some other studies. Side effects were mostly reduced appetite and headache. The tolerability of memantine, donepezil, and galantamine was all convincing.

Conclusions While galantamine did not demonstrate a promising efficacy in ADHD, memantine and donepezil showed effectiveness. However, future studies are needed to confirm their efficacy in ADHD since there was some inconsistency.

Keywords ADHD, Alzheimer's, Donepezil, Galantamine, Memantine, Rivastigmine

*Correspondence:
Ramin Abdi Dezfouli
Raminabdi77@gmail.com
Full list of author information is available at the end of the article

Introduction

Attention deficit hyperactivity disorder (ADHD) is defined as an early-onset neurodevelopmental disorder [1], with its key symptoms being lack of proper attention, hyperactivity, and impulsiveness [2]. It is estimated that 3.4% of children [3] and up to 5% of adults worldwide suffer from ADHD [4, 5]. Children with ADHD often struggle with tasks that require sustained attention, organization, and self-control [6]. These difficulties can impact their academic performance, social interactions, and overall quality of life. While the exact cause of ADHD is unknown, research suggests that it may involve a combination of genetic, environmental, and neurological factors [7]. Treatment for ADHD typically involves a multimodal approach that includes behavioral therapy, medication management, and support from parents and educators.

Regarding treatment approaches, while there exist non-pharmacological interventions such as behavioral therapies, cognitive training, game-based training, mindfulness, neurofeedback, and physical exercise [8], pharmacological interventions still remain the first-line therapy [9]. Psychostimulants such as methylphenidate are the first-line choice among medications, and second-line pharmacotherapies include non-stimulants like atomoxetine, clonidine, and guanfacine [10–12]. However, these medications have their own drawbacks. Due to the treatments' sympathomimetic nature, potential for abuse, and inability to induce a sufficient response in certain patients, there is always a need to find alternative pharmacotherapies for ADHD [13].

Although most of the common ADHD medications act by affecting the catecholamine pathways [14], some studies have suggested that glutamatergic and cholinergic systems can be of alternative targets for intervention [15–17]. It is hypothesized that a genetic and cell signaling link may exist between an *N*-methyl-D-aspartate (NDMA)-type glutamate receptors and ADHD [18, 19]. Moreover, the cholinergic system, particularly the nicotinic acetylcholine (ACh) receptors, is shown to be responsible for primary brain functions relevant to cognition, including motor activities, attention, and memory [20–22]. Therefore, it can be concluded that antagonizing NMDA receptors or increasing ACh concentration in the synapses by inhibiting its degradation by acetylcholinesterase (AChE) can help reduce symptoms of ADHD. NMDA-receptor antagonists and AChE inhibitors exist in the form of tablets, capsules, and oral solutions and are the primary medications that are used for the management of Alzheimer's disease (AD) [23]. While memantine stands as the primary NMDA receptor antagonist utilized in AD treatment, the key drugs within the AChE inhibitors class include donepezil, rivastigmine, and galantamine.

Since there exist scattered trials evaluating the efficacy of donepezil, rivastigmine, memantine, and galantamine in ADHD, and considering that some patients may be unable to tolerate side effects, be contraindicated to use, or be resistant to first-line ADHD treatments, the present systematic review aims to answer this question. In people with ADHD, are NMDA receptor antagonists and AChE inhibitors effective in decreasing disease symptoms compared to placebo?

Methods

The protocol for this study was authored and registered in PROSPERO (International Prospective Register of Systematic Reviews) and subsequently adhered to registration ID: CRD42023441473. The PRISMA protocols for writing systematic reviews [24] and abstracts [25] were followed.

Search strategy

The systematic search was conducted on Web of Science, PubMed, and Scopus until February 2023 by two independent researchers. The syntax used for searching each database, and the number of obtained results can be seen in Supplementary Table 1. While there was no restriction on the publication year, there was a restriction on publication language, and only English studies were searched. Publications that contained the search phrases in their title or abstract were imported into the EndNote reference manager. Duplicate studies were removed, and the screening stages were carried out by two independent researchers.

Eligibility criteria and study selection

Clinical trials assessing the efficacy of memantine, galantamine, donepezil, and rivastigmine in ADHD patients were the desired studies to be included during the first screening stage. Either reporting the reduction of ADHD symptoms as compared to placebo or as pre- and post-treatment were both desired. Two independent researchers carried out assessing obtained publications according to the goals of the study. Studies on other psychiatric diseases such as schizophrenia, toxicity studies, bio-equivalency studies, studies on controlling side effects of stimulants, and studies on assessing the safety and tolerability of drugs in other diseases were excluded during the first screening stage.

The exclusion criteria for the second screening stage were as follows: not clearly reporting the administration routine of medications, utilizing non-pharmaceutical interventions on top of medications, and using AD medications for treating other diseases of ADHD patients rather than their ADHD symptoms (i.e. substance abuse in ADHD patients).

Data extraction

Data were extracted from the final studies by two researchers independently. The abstracted data included studies' characteristics such as first author, year of publication, study location, participants' characteristics, dose and administration routine of medication, comparator arm and its administration routine, duration of the trial, the measure of outcome, side effects, number of patients left because of side effects, and final results about the improvement of symptoms. Outcomes' certainty was assessed utilizing the grade criteria [26]. Two independent reviewers utilized the Cochrane Collaboration tool to assess the risk of bias within the included studies [27].

Results

Study selection

A flowchart of the screening stages can be found in Fig. 1. As can be seen, 1597 articles were found in the initial search. Of those, 322 articles were from PubMed, 390 were from Scopus, and 885 were from Web of Science. When classified by drug, 759 articles were found for memantine, 200 for rivastigmine, 459 for donepezil, and 179 for galantamine. As can be inferred, memantine and donepezil seem to be more noticeable for ADHD. Five-hundred fifteen articles were removed as the result of excluding duplicate studies. During the first screening stage, 1068 articles were excluded due to reasons such as not being a clinical trial, not using anti-Alzheimer medications, and not investigating ADHD. Of the 14 articles that were screened by full text during the second screening stage, seven studies were for memantine, five were for donepezil, and two were for galantamine. It should be noted that there were no studies evaluating the efficacy of rivastigmine in ADHD patients, and hence, no outcomes for this medication are reported. During the second screening stage, one study from the memantine group was excluded because it was on attention deficit symptoms in Parkinson's patients [28]. One study was excluded from the donepezil group because it only assessed the side effects of donepezil [29], and one study from the galantamine group was excluded because it was about magnetic resonance imaging (MRI) [30]. Finally, 11 studies were retrieved for final inclusion, with 6 studies for memantine [31–36], 4 for donepezil [22, 37–39], and 1 for galantamine [40]. It is worth mentioning that two of the donepezil studies were actually case series. However, since they reported the desired data, they were included in the review.

Basic characteristics of the selected studies

Table 1 contains a comprehensive summary detailing the characteristics of all studies that were included in the analysis. As can be seen, of the six studies evaluating the efficacy of memantine in ADHD, three were conducted in Iran [33, 34, 36], and three were conducted in the United States (USA) [31, 32, 35]. Sample sizes varied among studies, with a range of 16–40. Three references [31, 34, 35] studied adults with mean ages ranging from 33.1 to 41.8, while the other three [32, 33, 36] studied children with mean ages ranging from 8.1 to 9.51. All the studies used the *Diagnostic and Statistical Manual of Mental Disorders 4th edition* (DSM-IV) [41] criteria as the base approach for diagnosing ADHD. Reference studies also used other criteria such as the Adult ADHD Investigator Symptom Report Scale (AISRS) [42], The Kiddie Schedule for Affective Disorders and Schizophrenia for School-Age Children-Present and Lifetime version (K-SADS-PL) [43], the Wender Utah Rating Scale (WURS) [44], and the Clinical Global Impression (CGI) [45] as secondary diagnosis approaches. References had relatively similar exclusion criteria, such as mental retardation ($IQ < 80$), unstable psychiatric conditions, alcohol or substance abuse, and pregnancy. All the participants in memantine clinical trials did not have any comorbidities.

As reported in Table 1, of four studies for donepezil, one was conducted in Spain [37], and one was conducted in the USA [38]. The other two references [22, 39] were actually case series studies. However, since the desired data and outcomes were efficiently reported, their data was used. Sample sizes varied among studies ranging from 5 to 13. While two references studied children and adolescents [37, 39], another study only included adolescents [22], and the last one studied children and adults [38]. All the references used the DSM-IV criteria for diagnosing ADHD. While there were no exclusion criteria for the case series studies, clinical trials excluded participants with serious health conditions. Some participants of donepezil clinical trials had some comorbidities such as tics, pervasive developmental disorder, and executive functioning deficits.

Finally, the only study that was retrieved for galantamine was conducted in the USA on 28 adult participants with a mean age of 35.9. Inclusion and exclusion criteria were mostly the same as in other reported trials. Participants of this study did not have any comorbidities.

Outcomes

The summary results of the included studies can be found in Table 2. In the memantine group, the first study [31] compared memantine with placebo (both arms were add-ons to methylphenidate) in adults for 14 weeks. Results showed that although the two strategies reduced the AISRS score by 0.29 standardized mean differences (SMDs), there was not a statistically significant

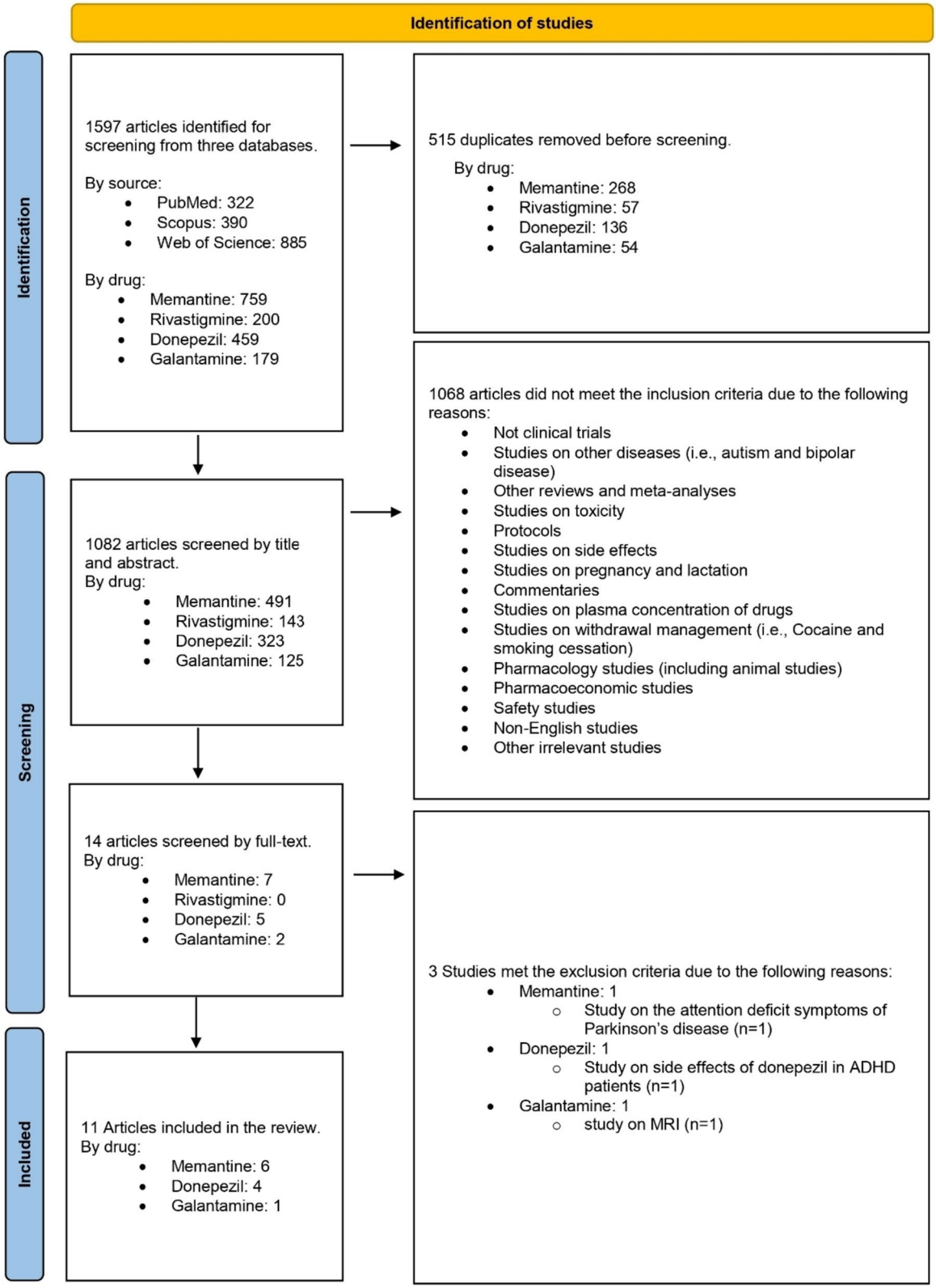

Fig. 1 **A** summary detailing the process of selecting studies for the research

Table 1 The basic characteristics of included studies

Author, year	Study location	Sample size	Studied population, mean age (range)	Inclusion criteria	Exclusion criteria
Memantine					
Biederman et al. (2017) [46]	USA	26	Adults, 15–57 (35.33)	• DSM-IV criteria • AISRS score ≥ 20	• Clinically significant chronic medical conditions • *IQ* < 80 • Any unstable psychiatric condition • Drug or alcohol abuse • Pregnant or nursing females
Findling et al. (2007) [32]	USA	16	Children, 6–12 (8.1)	• DSM-IV criteria • K-SADS-PL	• Any unstable psychiatric condition, except for oppositional defiant disorder • A general medical condition that might interfere with the conduct of the study
Riahi et al. (2020) [47]	Iran	39	Children 6–12 (9.51)	• DSM-IV criteria • Conner's score ≥ 20	• A serious psychiatric disorder • History of lack of response to memantine • History of severe side effects associated with memantine and methylphenidate
Mohammadi et al. (2015) [36]	Iran	40	Children, 6–11 (8.6)	• DSM-IV criteria • K-SADS-PL	• Other psychiatric disorders • Mental retardation (*IQ* < 70) • Clinically significant chronic medical condition • Current abuse or dependence on drugs in the last 6 months
Mohammadzadeh et al. (2019) [48]	Iran	40	Adults, 18–45 (33.1)	• Parents of ADHD children • DSM-IV • WURS	• Mental disability • The presence of any other psychiatric disorder • Substance or alcohol abuse (in a recent month) • Pregnant women • History of allergy to memantine • The presence of a serious medical illness
Surman et al. (2013) [35]	USA	34	Adults, 18–60 (41.8)	• DSM-IV • AISRS inattentive score ≥ 14 • CGI-S ≥ 4	• Any history of renal impairment, hepatic impairment, an organic brain disorder, a seizure disorder • *IQ* < 75 • Clinically unstable psychiatric conditions • History of substance dependence or abuse • Pregnant or nursing females
Donepezil					
Cubo et al. (2008) [37]	Spain	20	Children and adolescents, 7–17 (11.3)	• DSM-IV criteria	• Evidence of a secondary tic disorder • Mental retardation or autism • Diseases that would be expected to alter the safety profile of donepezil • All females of reproductive age were required to provide a negative urine pregnancy test
Doyle et al. (2006) [22]	NA (case series)	8	Adolescents, 10–17 (13.5)	• DSM-IV criteria	–
Wilens et al. (2000) [39]	NA (case series)	5	Children and adolescents, 8–17 (13.6)	• DSM-IV criteria	–

Table 1 (continued)

Author, year	Study location	Sample size	Studied population, mean age (range)	Inclusion criteria	Exclusion criteria
Wilens et al. (2005) [38]	USA	13	Children and adults (26)	• DSM-IV criteria	• Exclusionary comorbid conditions
Galantamine					
Biederman et al. (2006) [40]	USA	28	Adults, 18–55 (35.9)	• DSM-IV criteria	• Clinically significant chronic medical conditions • IQ lower than 80 • Clinically unstable psychiatric conditions • Drug or alcohol abuse or dependence within the 6 months preceding the study • Pregnant or breast-feeding women

Abbreviations: *DSM-IV* Diagnostic and Statistical Manual of Mental Disorders 4th edition, *WURS* Wender Utah Rating Scale, *CGI-S* Clinical Global Impression–ADHD-Severity Scale, *K-SADS-PL* The Kiddie Schedule for Affective Disorders and Schizophrenia for School-Age Children-Present and Lifetime version, *AISRS* Adult ADHD Investigator Symptom Report Scale, *NA* Not applicable

difference between the placebo group and the memantine group. There were some side effects related to using memantine: 41.7% of patients experienced decreased appetite, 50% experienced dry mouth, and 50% experienced headache. A total of 11.5% of patients left the trial because of side effects.

The second study for memantine [32] was an open trial in which children were given two doses of 10 mg/day and 20 mg/day for 8 weeks. Data were reported as the mean change from baseline (SD) at weeks 4 and 8. Results show that both doses reduced the severity of symptoms at week 4, with 20 mg/day being more effective (no data was reported about the statistical significance of results). The value of this decline in the symptoms also continued until week 8 for the 20 mg/day. Data for the 10 mg/day dose were not reported after the 4th week. Side effects included 25% nausea, 37.5% dizziness (for the 20 mg/day cohort), and 25% headache. There were no dropouts because of side effects.

The subsequent study [33] was also an open trial on children and had two groups. The first group had 0.1–0.25 mg/kg/day medication dosing, and the second group had 0.25–0.5 mg/kg/day dosing. Both groups were followed for 8 weeks, and although the Conners score was significantly reduced in both groups from baseline, there were no significant differences between the results of the two groups. In other words, both groups had the same effect. A total of 12.8% of participants left the trial because of side effects. The next study by Mohammadi et al. [36] used dosing of 10–20 mg/day for 6 weeks and used methylphenidate 20–30 mg/day as the comparator arm for children. Results showed that both protocols significantly reduced the symptoms, however, without any significant difference between the two groups. This study revealed that memantine exhibits comparable effectiveness to methylphenidate in managing ADHD. Side effects included 22% loss of appetite, 31% irritability, and 18% restlessness.

The fifth study [34] was a 6-week controlled trial comparing memantine 10 mg/day for the first week and 20 mg/day for the second week onwards with a placebo in adults. In this study, the memantine group's symptom reduction was significantly different from the symptom reduction in the placebo group, meaning that memantine is effective in reducing symptoms of ADHD. The final study in the memantine group [35] was a 12-week open-label trial. The dosing of memantine was 5 mg/day at baseline, followed by 5-mg BD (two times a day) at week 1, 15 mg/day at week 2, and 10-mg BD at week 3. The authors found a significant reduction in ADHD symptoms with mild–moderate side effects such as dizziness, lightheadedness, headache, and sedation. This study explicitly stated the absence of any cardiovascular side effects, such as alterations in blood pressure or heart rate.

Altogether, this conclusion can be drawn that memantine can effectively reduce ADHD symptoms. These studies have reasonable sample sizes and reported that memantine alone can significantly reduce disease symptoms. Even one study reported that memantine is as effective as methylphenidate. It may be concluded that memantine leads to improvements in ADHD symptoms. Moreover, it seems that the most frequent side effects were loss of appetite and headache. Results were a little inconsistent in the case of tolerability; while one study reported that no participant left due to side effects, another study had 21% of its participants left because of side effects. Overall, more trials are needed to obtain a more precise conclusion about the use of memantine in ADHD.

Table 2 Summary result of clinical trials assessing the efficacy of anti-Alzheimer drugs in ADHD

Author, year	Final medication administration routine[a]	Comparator arm	Other interventions	Trial duration	Result[b]	Side effect	Tolerability[b]
Memantine							
Biederman et al. (2014) [46]	10-mg BID	Placebo	Adjunct to methylphenidate	14 weeks	Similar responses were seen for participants on placebo and memantine (SMD = −0.29)	• 41.7% appetite decrease • 50% dry mouth • 50% headache	11.5%
Findling et al. (2007) [32]	10 mg/day	Pre- and posttreatment	-	8 weeks	Mean ADHD-IV total score change from baseline value was −3.5 at week 4	• 25% nausea • 37.5% dizziness (only 20 mg/day group) • 25% headache	0%
	20 mg/day				Mean ADHD-IV total score change from baseline value was −11.5 at week 4 and −16.5 at week 8		0%
Riahi et al. (2020) [47]	0.1 to 0.25 mg/kg 0.25 to 0.5 mg/kg	Pre- and posttreatment Pre- and posttreatment	Adjunct to methylphenidate	8 weeks 8 weeks	The mean scores of the Conner's score in both groups were significantly reduced. There was no significant difference between the two groups	• NR	12.8%
Mohammadi et al. (2015) [36]	10–20 mg/day	Methylphenidate 20–30 mg/day	-	6 weeks	A significant difference was observed at week 6 compared to baseline in both groups. There was not a significant difference between the two groups	• 22% loss of appetite • 31% irritability • 18% restlessness	-
Mohammadzadeh et al. (2019) [48]	20 mg/day	Placebo	-	6 weeks	There was a significant difference in the effect of drug and placebo changes	• NR	-
Surman et al. (2013) [35]	10-mg BID	Pre- and posttreatment	-	12 weeks	Each individual symptom of ADHD significantly improved	• 10% dizziness or lightheadedness, gastrointestinal, musculoskeletal, headache, and sedation	21.4%
Donepezil							
Cubo et al. (2008) [37]	10 mg/day with a 4-week washout period	Pre- and posttreatment	-	18 weeks	There was no significant improvement in any mean measure of ADHD	• 20% irritability • 20% gastrointestinal symptoms • 5% headache, sedation, nightmares, urinary incontinence, and dizziness	50%

Table 2 (continued)

Author, year	Final medication administration routine[a]	Comparator arm	Other interventions	Trial duration	Result[b]	Side effect	Tolerability[b]
Doyle et al. (2006) [22]	Daily dose of 2.5 to 30 mg	Pre- and posttreatment	-	18 weeks	All but one participant showed improvement	No side effects were reported	12.5%
Wilens et al. (2000) [38]	20 mg daily	Pre- and posttreatment	Adjunct to methylphenidate	14 weeks	There was a significant effect of donepezil in improving ADHD symptoms	Only one patient developed diarrhea which resolved after dose adjustment	-
Wilens et al. (2005) [38]	10 mg daily	Pre- and posttreatment	Adjunct to methylphenidate	12 weeks	There were no clinically or statistically significant reductions in the rating-scale measures of ADHD	• 85% gastrointestinal problems • 46% irritability • 38% appetite loss	23%
Galantamine							
Biederman et al. (2006) [40]	8–24 md daily	Placebo	-	12 weeks	There was no statistically or clinically significant greater reduction in either symptom cluster in the galantamine-treated patients relative to the placebo-treated subjects	• There were no differences between the galantamine- and placebo-treated subjects in the presence of any adverse effect	16%

[a] *OD* Once daily, *BD* Twice a day, *TDS* Three times a day

[b] Defined as percentage of patients who left the trial because of side effects

In the case of donepezil, the first study [37], which was an open-label 18-week study on children and adolescents, used donepezil dosing of 2.5 mg/day for 2 weeks, followed by 5 mg/day for the next 6 weeks, 10 mg/day for the last 6 weeks, and ended with a 4-week washout period. Study results showed no significant improvements in ADHD symptoms. Side effects included 20% irritability, 20% gastrointestinal symptoms, and 5% headache and sedation. The results of this study show that donepezil has a weak tolerability since 50% of patients left due to side effects. The second study [22] was a case series study. Subjects received donepezil dosages of 2.5–30 mg for 18 weeks. Regarding individual responses, nearly all participants exhibited improvement on the CGI-S scale, with only one individual not showing progress. Specifically, six out of the eight participants attained endpoint CGI-S scores of 1 or 2.

There were no side effects even in the child receiving the highest dose of 30 mg/daily. The subsequent study [39] was also a case series study. The treatment duration was 14 weeks, and donepezil (as an adjunctive therapy to methylphenidate) was started at a dosage of 2.5 mg/day and titrated up for a response (dosage did not pass 20 mg/day). The CGI-S ADHD scale showed a significant improvement, side effects were perfectly tolerated, and only one patient reported temporary diarrhea. Finally, the last study in the donepezil group [38] was a 12-week open clinical trial of 10 mg/day donepezil. While donepezil was used as an add-on therapy to methylphenidate, results showed that there was no statistically significant reduction in ADHD symptoms. Side effects included 85% gastrointestinal problems, 46% irritability, and 38% appetite loss in both children and adults. A total of 23% of patients left the trial due to side effects.

To summarize, results for donepezil are a little inconsistent. While two clinical trials reported that donepezil did not reduce symptoms, the two case series studies reported that donepezil alone and "donepezil + methylphenidate" significantly reduced symptoms. Moreover, while two references reported that donepezil did not lead to any side effects, two other studies reported that it caused irritability and gastrointestinal problems. It is prone to say that one of the trials reporting side effects used the combination of methylphenidate and donepezil, and therefore, the side effects may have occurred due to consuming methylphenidate. One study reported that 50% of participants left the trial due to the side effects.

As mentioned before, there was only one study for the galantamine group [40], and that was a 12-week controlled trial of galantamine compared to a placebo in adults. Galantamine was started with an initial dose of 8 mg/day for the first 4 weeks, followed by 16 mg/day for weeks 6 and 8 and 24 mg/day for weeks 10 and 12. Results showed that there was no statistically significant difference between the reduction of symptoms in the placebo and the galantamine group. Moreover, there also were no differences in the side effects of placebo and galantamine. Side effects of both groups were non-significant and were well tolerated.

Outcomes certainty

A complete list of all results and their certainty is reported in Table 3. As can be seen, after the assessment by GRADE criteria, results for using memantine and its tolerable side effects had high certainty. The main reasons for the reduction in certainty of donepezil results were inconsistency, indirectness (use of drugs as add-ons to methylphenidate), and the low number of references. Except for these results that had moderate certainty, all other results got low and very low levels of certainty:

1. Memantine significantly improves ADHD symptoms in children.
2. Memantine significantly improves ADHD symptoms in adults.
3. The side effects of memantine were not serious and were tolerable in children.
4. The side effects of memantine were not serious and were tolerable in adults.
5. Donepezil significantly improves ADHD symptoms.
6. The side effects of donepezil were not serious and were tolerable.
7. Anti-Alzheimer medications significantly improve ADHD symptoms.
8. The side effects of anti-Alzheimer medications were not serious and were tolerable.

Results about the effectiveness of galantamine in ADHD had very low certainties. The main aim of this study, which was the efficacy of anti-Alzheimer medications in ADHD, got moderate certainty. The detailed assessment of all other side conclusions and their certainty can be found in Table 3. Overall, it seems that anti-Alzheimer medications may be alternative treatments for ADHD. However, other clinical trials are needed to improve the reliability of their effectiveness in ADHD.

Risk-of-bias assessment

The outcomes of the risk-of-bias assessment conducted on the included studies are depicted in Fig. 2. As can be seen, all the studies had a low risk of bias in the selection domain, which consists of "random sequence generation" and "allocation concealment." In the performance bias (blinding of participants), all open trials had a high risk, all controlled trials had a low risk, and the two case series studies had an unclear risk. The results of the "detection bias" domain were the same. Except for four studies, all

Table 3 GRADE evidence profile: using memantine, donepezil, and galantamine in treating ADHD symptoms

Certainty assessment								Population size	Certainty
Outcome	**Number of studies**	**Study design**	**Risk of bias**	**Imprecision**	**Inconsistency**	**Indirectness**	**Publication bias**		
Memantine									
Memantine significantly improves ADHD symptoms in ADHD patients	5	RCT	NS	NS	NS	NS	NS	169	High
Memantine significantly improves ADHD symptoms in children	3	RCT	NS	S	NS	NS	NS	95	Moderate
Memantine significantly improves ADHD symptoms in adults	3	RCT	NS	S	NS	NS	NS	74	Moderate
The side effects of memantine in ADHD patients were not serious and were tolerable (no age range)	5	RCT	NS	NS	NS	NS	NS	169	High
The side effects of memantine in children ADHD patients were not serious and were tolerable	3	RCT	NS	S	NS	NS	NS	95	Moderate
The side effects of memantine in adult ADHD patients were not serious and were tolerable	3	RCT	NS	S	NS	NS	NS	74	Moderate
Methylphenidate and memantine are equal in efficacy for treating ADHD symptoms in children	1	RCT	NS	S	S	NS	NS	40	Very low
Placebo and memantine are equal in efficacy for controlling ADHD symptoms in adults	1	RCT	NS	S	S	NS	NS	26	Very low

Table 3 (continued)

Certainty assessment								Population size	Certainty
Outcome	**Number of studies**	**Study design**	**Risk of bias**	**Imprecision**	**Inconsistency**	**Indirectness**	**Publication bias**		
Donepezil									
Donepezil significantly improves ADHD symptoms (no age range)	4	RCT, CS	NS	NS	S	S	NS	46	Moderate
The side effects of donepezil in ADHD patients were not serious and were tolerable (no age range)	4	RCT, CS	NS	S	S	NS	NS	46	Moderate
Galantamine									
Galantamine does not differ ignificantly from placebo in reducing ADHD symptoms (no age range)	1	RCT	NS	S	S	NS	NS	28	Very low
The side effects of galantamine in ADHD patients were not serious and were tolerable (no age range)	1	RCT	NS	S	S	NS	NS	28	Very low
Anti-Alzheimer's medications									
Anti-Alzheimer's medications significantly improve ADHD symptoms	11	RCT, CS	NS	NS	S	S	NS	243	Moderate
The side effects of anti-Alzheimer medications in ADHD patients were not serious and were tolerable	11	RCT. CS	NS	NS	S	S	NS	243	Moderate

RCT Randomized clinical trial, *CS* Case series, *NS* Not serious, *S* Serious

the studies had a low risk of attrition bias. Finally, all studies had a low risk of selective reporting bias.

Discussion

This study aimed to evaluate anti-AD medications' potential as alternative agents for the management of ADHD. While our findings did not indicate promising efficacy for AChEIs except for donepezil, certain studies highlighted promising effects associated with the NMDA receptor antagonist, memantine.

In line with our study, Buoli et al. (2016) [49] conducted a systematic review of alternative pharmacological strategies for ADHD. They also reported the efficacy of memantine along with other agents like metadoxine,

Fig. 2 The outcomes derived from assessing the risk of bias among the studies included in the analysis

modafinil, and several antidepressants. Doses up to 20 mg/day of memantine were reported to improve symptoms significantly. However, as our study's results showed much inconsistency, the outcomes of that study also contradicted the findings of other controlled trials that did not show the superiority of memantine compared to placebo. Moreover, while one recent comprehensive review suggested memantine as an alternative [50], another study did not recommend memantine and galantamine as valid alternative therapies [49].

In the case of other non-stimulants, although several studies [49, 51–53] reported that bupropion has concrete evidence of efficacy as an alternative approach, other studies have concluded that other non-stimulants such as venlafaxine [54–58] or modafinil [59–61] have promising effectiveness with reasonable tolerability as well. Other studied alternative candidates were buspirone, duloxetine, and lithium, which showed some positive results but required further investigation since their efficacy was supported by only a limited number

of evidence [49, 50, 54, 62–69]. Although tricyclic antidepressants (TCAs) were also reported to be useful [70–73], they are not considered the drug of choice due to their risk of inducing arrhythmias, overdose, and other potential side effects [54]. It is important to note that all these medications are not recommended as initial treatment options and should be administered under the careful supervision of clinicians in ADHD management.

Possible mechanism of action

While there was no strong evidence that AChEIs are effective in ADHD, it is prone to study the mechanisms in which these medications may be effective in reducing ADHD symptoms. Studies have shown that individuals with ADHD often exhibit lower levels of ACh or dysregulation within the cholinergic system [74]. This imbalance can contribute to difficulties in sustaining attention [75, 76], inhibiting impulsive behaviors [77–79], and maintaining optimal cognitive performance [80, 81] since ACh is involved in various physiological processes such as muscle contraction, memory formation, and cognitive function. These mechanisms give a clear explanation of how AChEIs can be beneficial in ADHD. Studies have also found that ACh enhances the ability to filter out distractions and maintain sustained attention [82, 83]. In individuals with ADHD, who often struggle with maintaining focus and easily getting distracted, optimizing ACh levels is assumed to potentially improve their attention span, and this is another mechanism in which AChEIs are beneficial for ADHD patients. Finally, ACh plays a crucial role in regulating the activity of various brain regions, including the prefrontal cortex [84–86]. The prefrontal cortex is one of the main brain regions that is believed to have neurotransmitter dysfunctions in the pathophysiology of ADHD, and this is another possible mechanism for the efficacy of AChEI in ADHD.

Too much about AChEIs, NMDA receptors, a subset of glutamate receptors within the brain, hold a pivotal role in synaptic plasticity and learning processes. They govern the transmission of signals between neurons, which is crucial for cognitive functions like attention, memory, and executive control [84, 87–89]. Understanding the intricate interplay between ADHD and NMDA receptors may provide valuable insights into potential therapeutic interventions for this complex disorder.

First, glutamate receptors are known as excitatory neurotransmitters, and their blockade was shown to suppress the excitatory symptoms of ADHD [90]. Second, blocking NMDA receptors causes an increase in the prefrontal dopamine both in human and nonhuman subjects [91, 92], which is one of the main brain areas with dopamine deficiency in ADHD patients [93, 94]. The prefrontal cortex keeps shifting attention in check, which is proven to be dysregulated in ADHD patients [93, 95]. Moreover, dopamine has the role of inhibiting glutamatergic pathways in the prefrontal cortex which results in a decreased behavioral response [96–99]. Since ADHD patients have dopamine imbalances in their brains, it is assumed that ADHD patients also have glutamatergic overproduction, which in turn leads to high distractibility. As it is proven, the main dysregulation in the pathophysiology of ADHD is dopamine dysregulation, which leads to imbalances in other neurotransmitters, leading to disease symptoms.

Finally, the more the importance of the glutamatergic system in ADHD pathophysiology is revealed, the more it is suggested to assess the role of the gamma-aminobutyric acid (GABA) system in ADHD as well. There exist some studies hypothesizing the probable role of the GABA system in the impulsivity of ADHD patients [100, 101].

Is there a link between Alzheimer's disease and ADHD?

The connection between Alzheimer's disease and ADHD has been a topic of interest in several studies. While a direct connection is not established, some research hints at a slightly elevated risk of Alzheimer's later in life among individuals with ADHD [102, 103]. However, having ADHD does not equate to an inevitable development of Alzheimer's. Numerous factors contribute to the onset of the disease. For individuals with ADHD, managing symptoms is crucial in mitigating the risk of potential cognitive decline. It is important to note that while both conditions can affect cognitive function, they are distinct disorders with different underlying causes. Therefore, a proper diagnosis from a healthcare professional is crucial in order to provide appropriate treatment and support for individuals experiencing these symptoms.

Studies exploring the co-occurrence of both conditions have found some interesting connections. Indeed, a study has suggested a potential heightened risk of Alzheimer's among individuals with ADHD as they age [102]. The observed correlation might stem from shared genetic factors or overlapping underlying mechanisms between ADHD and Alzheimer's. Another study revealed that adults with ADHD exhibiting cognitive impairment symptoms were at a higher risk of developing Alzheimer's disease compared to those without such symptoms [104]. These findings underscore the significance of early detection and intervention for individuals with ADHD. Timely measures could potentially aid in preventing or delaying the onset of Alzheimer's disease. Additionally, it is of great importance to search for potential treatment strategies that target both conditions simultaneously, aiming to improve overall cognitive function and quality of life for individuals affected by both ADHD and Alzheimer's disease. Overall, there is a necessity for further research to comprehensively grasp the relationship between these

conditions and to devise effective interventions for those impacted by both ADHD and Alzheimer's.

Strengths, limitations, and suggestions for future works

This work has several strengths; it is the first systematic review with all of its focus on the use of anti-AD medications in ADHD. Its comprehensiveness in reporting the results is another positive point of this study; the efficacy, safety, and tolerability of drugs were precisely reviewed and reported. All the possible conclusions and outcomes were extracted and reported precisely (GRADE table), even if the certainties were very low. This paves the way for future researchers to identify areas that require further studies to increase the reliability of outcomes in treating ADHD symptoms.

However, there are some limitations to this work as well. Despite many efforts, a quantitative analysis was not possible due to the lack of reported quantitative data and because some studies used memantine as an add-on therapy. Another limitation is the high inconsistency and indirectness that existed among reference studies, leading to lowering the reliability of results. Future studies are needed to confirm the effectiveness of anti-AD drugs with other medications for ADHD.

Conclusion

While the AChEIs (donepezil and galantamine) did not demonstrate a promising efficacy in ADHD, the NMDA receptor antagonist (memantine) showed promising effects in some studies. However, it is hard to draw a conclusion since other studies reported it was ineffective in ADHD. Future studies are needed to confirm its efficacy in ADHD. There was not any data about using rivastigmine in ADHD.

Supplementary Information

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Additional file 1: Supplementary Table 1. The syntax used for searching each database and the number of results in February 2023.

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RAD and SA conducted the search and the screening stages. RAD and EE extracted data and designed tables. RAD drafted the paper. RAD was the supervisor.

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Declarations

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Not applicable.

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Competing interests
The authors declare that they have no competing interests.

Author details
[1]Chronic Diseases Research Center, Endocrinology and Metabolism Population Sciences Institute, Tehran University of Medical Sciences, Tehran, Iran. [2]Department of Pharmacy and Pharmaceutical Sciences, Tehran Islamic Azad University of Medical Sciences, Tehran, Iran. [3]Student Research Center, Science and Research Branch, Islamic Azad University, Tehran, Iran.

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