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## Could memantine be a treatment option for ADHD and ASD?

### Czy memantyna mogłaby być opcją leczenia w ADHD i ASD?

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#### Abstract

Memantine is a non-competitive *N*-methyl-D-aspartate receptor antagonist approved by the European Union and the U.S. Food and Drug Administration for the treatment of dementia and Alzheimer's disease. In recent years, reports have suggested memantine's potential efficacy in alleviating symptoms associated with attention deficit hyperactivity disorder and autism spectrum disorder. Current research indicates that one aetiological factor in these neurodevelopmental disorders may involve dysregulation of excitation/inhibition signalling in the nervous system, linked to dysfunctions in neuron–glia interactions. This review presents findings published to date on the safety and clinical efficacy of memantine in attention deficit hyperactivity disorder and autism spectrum disorder. The available literature is currently limited, consisting primarily of single randomised controlled trials and open-label studies conducted in small patient groups. The review includes publications involving participants aged 17 and older. In these studies, memantine was administered at doses ranging from 5 to 20 mg per day, either as monotherapy or as an adjunct to stimulant medication. Memantine appears to be a well-tolerated drug with few side effects. Preliminary results regarding its clinical efficacy are promising but do not yet support firm conclusions. Through this review, the authors aim to highlight the need for further methodologically rigorous studies in larger patient groups and to propose potential directions for future research.

**Keywords:** ADHD, ASD, drug therapy, neurodevelopmental disorders, memantine

#### Streszczenie

Memantyna jest niekompetycyjnym antagonistą receptora *N*-metylo-D-asparagianu zatwierdzonym przez Unię Europejską i amerykańską Agencję ds. Żywności i Leków do leczenia otępienia i choroby Alzheimera. W ostatnich latach pojawiły się doniesienia sugerujące potencjalną skuteczność memantyny w łagodzeniu objawów związanych z zespołem nadpobudliwości psychoruchowej z deficytem uwagi i zaburzeniami ze spektrum autyzmu. Obecne badania wskazują, że jednym z czynników etiologicznych tych zaburzeń neurorozwojowych może być dysregulacja sygnalizacji pobudzenia/hamowania w układzie nerwowym związana z dysfunkcjami w interakcjach neuron–glej. W przeglądzie przedstawiono opublikowane wyniki dotyczące bezpieczeństwa i skuteczności klinicznej memantyny w zespole nadpobudliwości psychoruchowej z deficytem uwagi i zaburzeniach ze spektrum autyzmu. Dostępne piśmiennictwo jest obecnie ograniczone i składa się głównie z pojedynczych randomizowanych badań kontrolowanych oraz badań otwartych prowadzonych w małych grupach pacjentów. W przeglądzie uwzględniono badania z udziałem uczestników w wieku  $\geq 17$  lat. W tych badaniach memantyna była podawana w dawkach 5–20 mg dziennie, w monoterapii lub jako dodatek do leków stymulujących. Memantyna wydaje się lekiem bezpiecznym, z niewielką liczbą działań niepożądanych. Wstępne wyniki dotyczące jej skuteczności klinicznej są obiecujące, ale nie pozwalają jeszcze na sformułowanie jednoznacznych wniosków. Poprzez niniejszy przegląd autorzy chcą podkreślić potrzebę dalszych rygorystycznych metodologicznie badań z udziałem większych grup pacjentów i zaproponować potencjalne strategie przyszłych badań.

**Słowa kluczowe:** ADHD, ASD, farmakoterapia, zaburzenia neurorozwojowe, memantyna

## INTRODUCTION

In recent years, increasing evidence has suggested that an imbalance between excitatory (glutamatergic, Glu) and inhibitory (gamma-aminobutyric acid, GABAergic) (E/I) neurotransmission might play a significant role in the pathophysiology of attention deficit hyperactivity disorder (ADHD) (Mamiya et al., 2021) and autism spectrum disorder (ASD) (Blatt et al., 2011; Nair et al., 2022; Siegel-Ramsay et al., 2021). Recent findings have indicated that Glu may be involved in the pathophysiology of ADHD due to its regulation of dopamine release through neuronal interactions between the prefrontal cortex (PFC) and the striatum (Warton et al., 2009). Alterations in glutamatergic signalling have been linked to ADHD symptoms in both animal models (Cheng et al., 2017) and human studies (Ulu et al., 2024; Vidor et al., 2022). Furthermore, Ulu et al. (2024) provided evidence linking *N*-methyl-D-aspartate-type glutamate receptors (NMDARs) to ADHD. These findings are further supported by earlier results from cell signalling studies (Kotecha et al., 2002; Surman et al., 2013) and genetic studies (Surman et al., 2013; Turic et al., 2004). On the other hand, postmortem studies of the brains of individuals with ASD have reported reduced expression of glutamatergic markers and changes in the morphometry of minicolumns, particularly within the dorsolateral PFC (Fetit et al., 2021; Nair et al., 2022). Postmortem studies have also identified the cerebellum as a key region exhibiting alterations in both glutamatergic and GABAergic neurotransmission in individuals with ASD (Fetit et al., 2021; Nair et al., 2022; Purcell et al., 2001). Moreover, findings from animal models of autism have provided evidence that cerebellar GABAergic dysfunction may directly influence Glu transmission and release in the PFC (McKimm et al., 2014; Nair et al., 2022).

It has been theorised that the E/I imbalance in ADHD and ASD may result from dysfunction in neuron–glia interactions (Kim et al., 2020). Disruption in normal functioning of astrocytes may contribute to the imbalance between E/I signalling due to their role in the glutamate–glutamine cycle (GGC). Astrocyte-derived glutamine (Gln) serves as a precursor for two major neurotransmitters in the central nervous system (CNS): the excitatory neurotransmitter glutamate (Glu) and the inhibitory neurotransmitter gamma-aminobutyric acid (GABA). Both Glu and GABA can also act as alternative substrates in CNS metabolism, enabling metabolic coupling between astrocytes and neurons via the GGC (Dąbrowska-Bouta et al., 2023). Excessive activation of glial cells initiates widespread inflammation in the brain, potentially leading to the elimination of synapses and impaired synaptic plasticity (Patterson, 2015). As part of this response, proinflammatory cytokines can trigger excitotoxicity via an increase in Glu release (Ashwood et al., 2011). This leads to overactivation of NMDARs, which is associated with neurotoxicity and neurodegeneration (Kwon and Koh, 2020). Although no

glutamatergic drugs are currently approved for ADHD and ASD, ongoing clinical trials are examining the efficacy of pharmaceuticals targeting E/I imbalance. One such drug is memantine (MEM), a low-affinity, voltage-dependent, non-competitive NMDAR antagonist, approved by the European Union and the U.S. Food and Drug Administration for the treatment of dementia and Alzheimer's disease (Dąbrowska-Bouta et al., 2023). Preclinical data indicate that MEM can additionally modulate other ion channels, acting as a non-competitive antagonist of nicotinic acetylcholine receptors, a non-competitive antagonist of type 3 serotonin receptors, an agonist of sigma-1 receptors, and an agonist of dopamine D2 receptors (Maskell et al., 2003; Peeters et al., 2004; Reiser et al., 1988; Seeman et al., 2008). However, this review primarily focuses on its influence on E/I imbalance associated specifically with Glu and GABA. It has been reported that MEM blocks extrasynaptic NMDARs more effectively than synaptic NMDARs (Léveillé et al., 2008). Nonetheless, the basis for this preferential NMDAR inhibition depending on subcellular location has not been systematically explored (Glasgow et al., 2017). MEM only binds to NMDARs when the calcium channel is pathologically activated by excessive Glu concentrations in the synaptic cleft (Folch et al., 2018). As a result, the drug prevents NMDA-mediated massive influx of  $\text{Ca}^{2+}$  into neurons, thereby blocking the initiation of cascading pathways that ultimately result in cell death (Matsunaga et al., 2015). By modulating the activation of NMDARs, MEM positively affects the expression and function of Glu transporters, as well as the activity of Glu transport in neuronal and glial fractions (Sulkowski et al., 2014). After blocking the NMDAR, MEM is rapidly displaced due to its low affinity. This property prevents prolonged receptor blockade and consequently reduces the adverse effects on learning and memory that are often associated with high-affinity NMDAR antagonists (Rogawski and Wenk, 2003). Furthermore, it has been suggested that MEM may influence the disrupted interactions among Gln, Glu, and GABA (Dąbrowska-Bouta et al., 2023). In this review, we summarise the available data on MEM, focusing on its safety and clinical efficacy as a potential off-label treatment for ASD and ADHD in adults.

## MATERIALS AND METHODS

The PubMed database search was conducted up to March 2024 using the following search term combinations: ('ADHD' OR 'attention deficit hyperactivity disorder' OR 'autism spectrum disorder' OR 'ASD') AND ('memantine'). Additionally, articles referenced in the initially identified publications were screened. Only studies published in English were considered for this review. Of the 56 identified publications, 14 were deemed relevant for inclusion. Given the limited number of studies available, both randomised controlled trials (RCTs) and open-label studies were included. Of the 14 relevant publications, 9 were excluded due to their

focus on paediatric populations. Ultimately, 5 articles, published from 2013 to 2022, met the eligibility criteria for the safety and clinical efficacy review.

## RESULTS

### Safety

In most trials, MEM was administered twice a day at a maximum dose of 20 mg/day (Joshi et al., 2016; Mohammadzadeh et al., 2019; Surman et al., 2013). Data on the side effects of MEM in adults with ADHD and ASD are limited. However, none of the trials reported any severe adverse events (AEs) (Biederman et al., 2017; Joshi et al., 2016; Mohammadzadeh et al., 2019; Nair et al., 2022; Surman et al., 2013). A summary of AEs occurring in more than 10% of participants is provided in Tab. 1.

In summary, the most frequently reported AEs included dizziness/light-headedness, gastrointestinal disturbances, musculoskeletal issues, headaches, and sedation (Joshi et al., 2016; Mohammadzadeh et al., 2019; Surman et al., 2013). Only the study by Nair et al. (2022) did not provide a detailed analysis of AEs associated with MEM use. However, it reported that two participants experienced

worsening behavioural symptoms. No other AEs were declared in that study (Nair et al., 2022). Dropout rates across the trials ranged from 0% to 20%, depending on the specific study (Biederman et al., 2017; Joshi et al., 2016; Mohammadzadeh et al., 2019; Nair et al., 2022; Surman et al., 2013). A comparison of discontinuation data is provided in Tab. 2. In the RCT by Biederman et al. (2017), MEM was used as an add-on therapy to osmotic release oral system-methylphenidate (OROS-MPH). The most common AEs observed significantly more frequently in the MEM + OROS-MPH group included decreased appetite, light-headedness, sweaty palms, and perceptual changes. A comprehensive comparison of AEs is presented in Tab. 1. Due to AEs, three participants discontinued the treatment. Of these, two (16.6%) were in the MEM + OROS-MPH group. One individual experienced increased anxiety and light-headedness, while the other reported heightened anxiety along with vision changes (Biederman et al., 2017). Further information on dropout rates can be found in Tab. 2.

### Clinical efficacy in ADHD

At the time of writing, only a few trials investigating the impact of MEM on adult individuals diagnosed with ADHD

| Author, publication date                                                                      | Common adverse event           |                    | Number of participants (%)                                                |                    |
|-----------------------------------------------------------------------------------------------|--------------------------------|--------------------|---------------------------------------------------------------------------|--------------------|
| Nair et al., 2022                                                                             | Worsening behavioural symptoms |                    | 2 (20%)                                                                   |                    |
| Joshi et al., 2016                                                                            | Headache                       |                    | 2 (11%)                                                                   |                    |
| Surman et al., 2013                                                                           | Dizziness/Light-headedness     |                    | 8 (24%)                                                                   |                    |
|                                                                                               | Musculoskeletal issues         |                    | 6 (18%)                                                                   |                    |
|                                                                                               | Gastrointestinal issues        |                    | 6 (18%)                                                                   |                    |
|                                                                                               | Headache                       |                    | 5 (15%)                                                                   |                    |
|                                                                                               | Sedation                       |                    | 4 (12%)                                                                   |                    |
| Mohammadzadeh et al., 2019                                                                    | Dizziness                      |                    | No significant difference between MEM and placebo group – number (%) n/sw |                    |
|                                                                                               | Confusion                      |                    |                                                                           |                    |
|                                                                                               | Constipation                   |                    |                                                                           |                    |
|                                                                                               | Back pain                      |                    |                                                                           |                    |
|                                                                                               | Drowsiness/Sleepiness          |                    |                                                                           |                    |
| Biederman et al., 2017                                                                        | MEM + OROS-MPH                 | OROS-MPH (placebo) | MEM + OROS-MPH                                                            | OROS-MPH (placebo) |
|                                                                                               | Dry mouth                      |                    | 6 (50%)                                                                   | 6 (42.9%)          |
|                                                                                               | Appetite decrease              |                    | 5 (41.7%)                                                                 | 1 (7.1%)           |
|                                                                                               | Insomnia                       |                    | 3 (25%)                                                                   | 6 (42.9%)          |
|                                                                                               | Palpitations                   |                    | 4 (33.3%)                                                                 | 3 (21.4%)          |
|                                                                                               | Fatigue                        |                    | 4 (33.3%)                                                                 | 3 (21.4%)          |
|                                                                                               | Light-headedness               | –                  | 2 (16.7%)                                                                 | 0 (0%)             |
|                                                                                               | Anxiety                        |                    | 2 (16.7%)                                                                 | 2 (14.3%)          |
|                                                                                               | Nausea                         |                    | 2 (16.7%)                                                                 | 1 (7.1%)           |
|                                                                                               | Sweaty palms                   | –                  | 2 (16.7%)                                                                 | 0 (0%)             |
|                                                                                               | Perceptual changes             | –                  | 2 (16.7%)                                                                 | 0 (0%)             |
|                                                                                               | –                              | Chest discomfort   | 0 (0%)                                                                    | 2 (14.3%)          |
|                                                                                               | Jitteriness                    |                    | 2 (16.7%)                                                                 | 4 (28.6%)          |
|                                                                                               | Head discomfort                |                    | 1 (8.3%)                                                                  | 3 (21.4%)          |
| MEM – memantine; n/s – not specified; OROS-MPH – osmotic release oral system-methylphenidate. |                                |                    |                                                                           |                    |

MEM – memantine; n/s – not specified; OROS-MPH – osmotic release oral system-methylphenidate.

Tab. 1. Summary of commonly reported adverse events of memantine

| Author, publication date                                                                     | Reason for discontinuation              |                    | Number of participants (%) |                    | Total number of participants who discontinued (%) |                    |
|----------------------------------------------------------------------------------------------|-----------------------------------------|--------------------|----------------------------|--------------------|---------------------------------------------------|--------------------|
| Nair et al., 2022                                                                            | Worsening behavioural symptoms          |                    | 2 (20%)                    |                    | 2 (20%)                                           |                    |
| Joshi et al., 2016                                                                           | Treatment-limiting adverse events (n/s) |                    | 1 (5.6%)                   |                    | 1 (5.6%)                                          |                    |
| Surman et al., 2013                                                                          | Impaired concentration                  |                    | 2 (5.9%)                   |                    | 6 (17.5%)                                         |                    |
|                                                                                              | Elevated systolic blood pressure        |                    | 1 (2.9%)                   |                    |                                                   |                    |
|                                                                                              | Fatigue                                 |                    | 1 (2.9%)                   |                    |                                                   |                    |
|                                                                                              | Mood changes and impaired concentration |                    | 1 (2.9%)                   |                    |                                                   |                    |
|                                                                                              | Blurry vision                           |                    | 1 (2.9%)                   |                    |                                                   |                    |
| Mohammadzadeh et al., 2019                                                                   | MEM                                     | Placebo            | MEM                        | Placebo            | MEM                                               | Placebo            |
|                                                                                              | –                                       |                    | 0 (0%)                     |                    | 0 (0%)                                            |                    |
| Biederman et al., 2017                                                                       | MEM + OROS-MPH                          | OROS-MPH (placebo) | MEM + OROS-MPH             | OROS-MPH (placebo) | MEM + OROS-MPH                                    | OROS-MPH (placebo) |
|                                                                                              | Increased anxiety and light-headedness  | –                  | 1 (8.3%)                   | –                  | 2 (16.6%)                                         | 1 (7.1%)           |
|                                                                                              | Increased anxiety and vision changes    | –                  | 1 (8.3%)                   | –                  |                                                   |                    |
|                                                                                              | –                                       | Hand twitching     | –                          | 1 (7.1%)           |                                                   |                    |
| MEM – memantine; n/s – not specified; OROS-MPH – osmotic release oral system-methyphenidate. |                                         |                    |                            |                    |                                                   |                    |

**MEM** – memantine; **n/s** – not specified; **OROS-MPH** – osmotic release oral system-methylphenidate.

Tab. 2. Summary of treatment discontinuation data in memantine trials

have been conducted. A summary of the analysed trials is provided in Tab. 3.

The studies by Surman et al. (2013) and Mohammadzadeh et al. (2019) reported statistically significant improvements in ADHD symptoms. Furthermore, Surman et al. (2013) found statistically significant improvements in neuropsychological performance and executive function (EF) deficits. However, the number of participants in both studies was limited – 34 in the study by Surman et al. (2013) and 40 in the study by Mohammadzadeh et al. (2019). Notably, only the study by Mohammadzadeh et al. (2019) was an RCT, which provides stronger evidence due to its more rigorous design. Although the RCT by Biederman

et al. (2017) did not report a statistically significant response to MEM as adjunctive therapy to stimulants, some improvements were noted in selective areas of EF, along with better regulatory control over emotions and behaviours (Biederman et al., 2017). These findings highlight the need for further research with larger groups of participants, as the study by Biederman et al. (2017) included only 26 participants.

### Clinical efficacy in ASD

There has been only one trial investigating the impact of MEM on adults diagnosed with ASD. Another study

| Author, publication date   | Type of trial                                       | Enrolled subjects                       | Target dose of MEM                                  | Main results at the end of trial                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                |
|----------------------------|-----------------------------------------------------|-----------------------------------------|-----------------------------------------------------|---------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| Surman et al., 2013        | 12-week open label trial                            | N = 34<br>18–60 y/o<br>F – 9<br>M – 25  | 15–20 mg/day (max. 10 mg BID)                       | <ul style="list-style-type: none"> <li>• AISRS: 44% of participants ≥30% reduction; total ADHD symptom reduction of 17.5 points (<math>p &lt; 0.001</math>); significant reductions in inattentive symptoms (–10.6) and hyperactive symptoms (–6.9)</li> <li>• CGI-S: 44% of subjects rated as much or very much improved</li> <li>• BRIEF-A: improvement across all subscales (<math>p &lt; 0.001</math>)</li> <li>• CANTAB: improvement in SWM total errors scaled (<math>p &lt; 0.05</math>); RVP A' (<math>p &lt; 0.05</math>); AGN total commissions (<math>p &lt; 0.001</math>); IED total errors adjusted (<math>p &lt; 0.05</math>); VRM free recall total correct (<math>p &lt; 0.001</math>); RTI simple reaction time declined (<math>p &lt; 0.05</math>)</li> </ul> |
| Mohammadzadeh et al., 2019 | 6-week RCT                                          | N = 40<br>18–45 y/o<br>F – 34<br>M – 6  | 20 mg/day (10 mg BID)                               | <ul style="list-style-type: none"> <li>• CAARS-S:S: improvement on MEM in Inattention/Memory Problems, Hyperactivity/Restlessness, Impulsivity/Emotional Lability, ADHD index (<math>p &lt; 0.001</math>)</li> </ul>                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                            |
| Biederman et al., 2017     | 12-week RCT added to open-label trial with OROS-MPH | N = 26<br>18–57 y/o<br>F – 14<br>M – 12 | 10 mg/day ± 5 mg at each visit as needed (5 mg BID) | <ul style="list-style-type: none"> <li>• AISRS: no significant differences between placebo and MEM (<math>p = 0.67</math>)</li> <li>• BRIEF-A GEC: no significant differences between placebo and MEM (<math>p = 0.95</math>), however 50% of participants improved their scores compared to 20% in the placebo group</li> <li>• BRIEF-A BRI: trend improvements favouring MEM in Inhibit (SMD = 1.07) and Self-Monitor (SMD = 0.56) subscales</li> <li>• CANTAB: no significant improvements on MEM or placebo</li> </ul>                                                                                                                                                                                                                                                      |

**AGN** – inhibitory control to affective stimuli of positive valence; **AISRS** – Adult ADHD Investigator Symptom Report Scale; **BID** – bis in die; **BRI** – Behavioral Regulation Index; **BRIEF-A** – Behavior Rating Inventory of Executive Function – Adult Version; **CAARS-S:S** – Conners' Adult ADHD Rating Scale – Short Self-Report; **CANTAB** – Cambridge Neuropsychological Test Automated Battery; **CGI-S** – Clinical Global Impression of Severity; **F** – female; **GEC** – Global Executive Composite; **IED** – Intra-Extra Dimensional Set Shifting; **M** – male; **MEM** – memantine; **mg** – milligrams; **N** – number; **OROS-MPH** – osmotic release oral system-methylphenidate; **RCT** – randomised controlled trial; **RTI** – reaction time; **RVP** – rapid visual information processing; **SWM** – spatial working memory; **VRM** – verbal recognition memory; **y/o** – years old.

| Author, publication date | Type of trial            | Enrolled subjects                      | Target dose of MEM            | Main results at the end of trial                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                   |
|--------------------------|--------------------------|----------------------------------------|-------------------------------|------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| Joshi et al., 2016       | 12-week open-label trial | N = 19<br>18–47 y/o<br>F – 5<br>M – 14 | 15–20 mg/day (max. 10 mg BID) | <ul style="list-style-type: none"> <li>• SRS-A-Total: improvement (<math>p &lt; 0.001</math>)</li> <li>• MGH-ASD-RS-Total: improvement (<math>p &lt; 0.001</math>)</li> <li>• BPRS-ASD: improvement (<math>p = 0.002</math>)</li> <li>• G/ASD CGI-I: 83% of subjects – score 2 or less</li> <li>• ADHD-SCL: improvement (<math>p &lt; 0.001</math>)</li> <li>• BAI: improvement (<math>p = 0.006</math>)</li> <li>• BDI: improvement (<math>p = 0.008</math>)</li> <li>• HAM-A: improvement (<math>p = 0.039</math>)</li> <li>• HAM-D, Y-BOCS, YMRS: no significant improvements</li> <li>• GAF: improvement (<math>p &lt; 0.001</math>)</li> <li>• BRIEF-A T-scores: statistically significant improvement of medium ES in GEC (<math>p = 0.015</math>); BRI (<math>p = 0.02</math>); MI (<math>p = 0.03</math>)</li> <li>• CANTAB significant improvement in: SWM between errors (<math>p = 0.005</math>); RTI 5 choice (<math>p = 0.001</math>); RTI simple (<math>p = 0.014</math>); AGN for positive stimuli (<math>p = 0.011</math>)</li> <li>• DANVA2: significantly reduced mean numbers of errors in identifying emotions by facial expression (<math>p = 0.003</math>), but not by tone of voice (<math>p = 0.9</math>); significant reduction in error frequency for low-intensity expression of emotions (<math>p = 0.028</math>), but not for high-intensity expression of emotions (<math>p = 0.1</math>)</li> </ul> |
| Nair et al., 2022        | 12-week open-label trial | N = 10<br>17–32 y/o<br>F – 1<br>M – 9  | 20 mg/day                     | <ul style="list-style-type: none"> <li>• 1H-MRS: no significant difference in Glx in LDLPFC* and R posterolateral cerebellum in responders and non-responders** (weak trend for ↑ LDLPFC Glx in responders – <math>p = 0.1</math>); ↑ NAA in LDLPFC in responders (<math>p = 0.024</math>)</li> <li>• Changes in CGI-I social scores: no significant correlation with Glx in LDLPFC (<math>p = 0.24</math>) and R posterolateral cerebellum (<math>p = 0.55</math>)</li> <li>• Predictors of ↓ post-treatment CGI-I social scores in linear hierarchical regression model: ↑ Glx in LDLPFC (<math>p = 0.025</math>), ↓ Ins in LDLPFC (<math>p = 0.04</math>)</li> <li>• Predictors of ↓ post-treatment SRS total score: ↑ Cr+PCr in LDLPFC (<math>p = 0.04</math>)</li> </ul>                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                      |

\* Very limited number of participants with high quality data for the LDLPFC in the non-responder, but  $p$ -value suggests that a larger sample size may reach statistical significance.  
\*\* CGI-I social scores were used to classify responders and non-responders.  
**1H-MRS** – proton magnetic resonance spectroscopy; **ADHD-SCL** – ADHD Symptom Checklist; **AGN** – inhibitory control to affective stimuli of positive valence; **ASD** – autism spectrum disorder; **BAI** – Beck Anxiety Inventory; **BDI** – Beck Anxiety Inventory; **BID** – bis in die; **BRI** – Behavioral Regulation Index; **BPRS** – Brief Psychiatric Rating Scale Autism Spectrum Disorder; **BRIEF-A** – Behavior Rating Inventory of Executive Function-Adult Version; **CANTAB** – Cambridge Neuropsychological Test Automated Battery; **CGI-S** – Clinical Global Impression of Severity; **Cr+PCr** – creatine+phosphocreatine; **DANVA2** – Diagnostic Analysis of Nonverbal Accuracy Scale; **ES** – effect size; **F** – female; **G/ASD CGI-I** – Clinical Global Impression-Severity Scale for Global Autism Spectrum Disorder; **GAF** – Global Assessment of Functioning Scale; **GEC** – Global Executive Composite; **Glx** – glutamate+glutamine; **HAM-A** – Hamilton Anxiety Scale; **HAM-D** – Hamilton Depression Scale; **Ins** – myo-inositol; **LDLPFC** – left dorsolateral prefrontal cortex; **M** – male; **MEM** – memantine; **mg** – milligrams; **MGH-ASD-RS** – Mass General Autism Spectrum Disorder Rating Scale; **MI** – Metacognition Index; **N** – number; **NAA** – N-acetylaspartate; **R** – right; **RTI** – reaction time; **SRS** – Social Responsiveness Scale; **SRS-A** – Social Responsiveness Scale-Adult Research Version; **SWM** – spatial working memory; **Y-BOCS** – Yale Brown Obsessive Compulsive Scale, **YMRS** – Young Mania Rating Scale; **y/o** – years old.

Tab. 4. Comparison of trials with memantine conducted in individuals with ASD

analysed the relationship between glutamatergic neurometabolites detected by magnetic resonance spectroscopy and changes in social behaviour. For accuracy, it needs to be pointed out that this study also included participants younger than adults, with the youngest being 17 years old. A summary of both trials is provided in Tab. 4.

The participants enrolled in the study by Joshi et al. (2016) were 19 intellectually capable adults with ASD, with a full-scale intellectual quotient (IQ) of  $106 \pm 15$ . Joshi et al. (2016) reported significant improvements in reducing the severity of ASD traits, as well as in ameliorating the severity of symptoms of comorbid ADHD, anxiety, and in cognition and EF. However, it is important to note that this study had a limited number of participants and lacked a more rigorous, placebo-controlled design.

Preliminary findings from Nair et al. (2022) on the relationship between glutamatergic neurometabolite levels and changes in social behaviour suggest that responsiveness to MEM may vary among individuals with ASD. According to Nair et al. (2022), elevated glutamatergic levels, combined with changes in glial and cellular energy metabolism markers in the left dorsolateral prefrontal cortex (DLPFC), could lead to greater improvements with MEM. However, larger

sample sizes are necessary to confirm these findings and to clarify the relationship between Glx (and other neurometabolites) and treatment response, since the study by Nair et al. (2022) enrolled only 10 participants.

## DISCUSSION

Since MEM has demonstrated a role as a glutamatergic modulator, its potential use in neuropsychiatric conditions has been suggested. This review explores the possible benefits of MEM in ADHD and ASD in adult individuals, based on its impact on the E/I imbalance implicated in the pathophysiology of these disorders (Kim et al., 2020). The analysed trials confirmed that MEM administration does not cause serious AEs (Biederman et al., 2017; Joshi et al., 2016; Mohammadzadeh et al., 2019; Surman et al., 2013). Studies in adults with ADHD reported that administration of MEM alone is beneficial, raising the hypothesis that MEM may become an alternative treatment option to stimulant medication (Mohammadzadeh et al., 2019; Surman et al., 2013). Furthermore, trends observed in the study by Biederman et al. (2017) provide a foundation for further research on the efficacy of MEM as add-on therapy to stimulants.



Future studies should also examine whether the two agents have a synergistic effect, as current results are insufficient, and more well-designed clinical trials with a larger pool of participants are needed.

The study by Joshi et al. (2016), conducted on intellectually capable adults with ASD, indicated that MEM may be an effective treatment alternative. However, as it was an open-label trial, without placebo control, the findings should be interpreted cautiously. Nevertheless, the findings from the study by Joshi et al. (2016) suggest that intellectual functioning within or above the average IQ score may contribute to the efficacy of MEM, especially since a previous review by Brignell et al. (2022) found no significant improvement in children with lower mean IQ scores.

The study by Nair et al. (2022), though also limited by a small pool of participants, offered a possible explanation for individual differences in responsiveness to MEM treatment, suggesting that different subsets of ASD may exist. Nair et al. (2022) implied that the efficacy of MEM may be influenced by individual differences, highlighting the need for a more refined and personalised approach to studying its potential benefits in this population of patients. Furthermore, these findings suggest the possibility of using proton magnetic resonance spectroscopy as a tool to identify potential biomarkers predictive of treatment response in ASD (Nair et al., 2022). It also needs to be noted that a larger pool of participants may provide an opportunity to explore whether factors such as intellectual functioning are also linked to the responsiveness to MEM treatment. Currently, due to limited data, further RCTs are needed to evaluate the long-term safety and efficacy of MEM in individuals with ADHD and ASD.

## CONCLUSION

Although some studies on MEM have indicated its safety and efficacy in ameliorating symptoms associated with ADHD and ASD in adults, the evidence remains insufficient. The reported benefits require further validation through large-sample RCTs before widespread use of MEM can be endorsed. Nevertheless, if future research confirms its efficacy, MEM might serve as an appealing treatment option for individuals with ADHD, ASD, or both.

### Conflict of interest

*The authors do not report any financial or personal connections with other persons or organisations which might negatively affect the content of this publication and/or claim authorship rights to this publication.*

### Author contribution

*Original concept of study; writing of manuscript: AS. Collection, recording and/or compilation of data; analysis and interpretation of data: AS, OM. Critical review of manuscript: MFL. Final approval of manuscript: AS, MFL.*

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