Table 1.

Summary of Findings From Studies Using Memantine in Pediatric and Adult Patients With ADHD

Author, year, country	Study design and setting	Target patients	Diagnostic criteria for ADHD	Inclusion criteria	Exclusion criteria	Duration	Number of patients (male/female)	Age, mean±SD, y	Intervention (drug type, dosing)	Outcome, mean (SD)	Adverse effects, N (%)	Final conclusion	Notes
Studies of pediatric patients with ADHD													
Findling et al,[67] 2007, US	Open-label, dose-finding, 8-wk trial at University Hospitals of Cleveland	Pediatric patients 6–12 y old with combined type ADHD	*DSM-IV-TR* and K-SADS-PL	Diagnosis of combined type ADHD with scores on ADHD-IV (≥24), CGI-S (≥4), PPVT ≥70, and normal physical examination, laboratory finding, electrocardiogram, β-human chorionic gonadotropin	Primary diagnosis: only patients with combined type ADHD were included, excluding other primary psychiatric diagnoses except oppositional defiant disorder. Neurological conditions: Individuals with neurological diseases such as epilepsy or Tourette disease were excluded. Medical conditions: Any significant medical conditions that could interfere with the study or pose a risk to the participant led to exclusion. Medication and therapy: Patients who had not properly washed out psychoactive medications or were undergoing psychotherapy changes were excluded.	8 wk after a 2-wk screening period	Cohort 1 8 (3/5) Cohort 2 8 (6/2)	Cohort 1 −10 mg/d of memantine 7.6 (6–10, min–max) Cohort 2 −20 mg/d of memantine 8.6 (6–12, min–max)	Once-daily morning dose of memantine oral solution (2 mg/mL), with or without food, titrated over a 4-wk period to a target dose of 10 mg/d (Cohort 1) Titrated over a 4-wk period to a once-daily memantine dose of 20 mg/d (Cohort 2)	Cohort 1 Baseline (SD)/final (SD) CGI-S rating 4.6 (0.52)/4.3 (0.71) ADHD-RS-IV-I 21.0 (5.68)/18.9 (6.20) ADHD-RS-IV-H 23.6 (2.07)/22.0 (2.62) ADHD-RS-IV total score −3.8 (2.31) Cohort 2 Baseline (SD)/final (SD) CGI-S rating 4.5 (0.53)/3.3(1.04) ADHD-RS-IV -I 21.9 (4.82)/18.6 (7.09) ADHD-RS-IV -H 20.0 (4.90)/14.3 (7.74) ADHD-RS-IV total score −9.0 (10.00)	Patients with ≥1 TEAE Cohort 1: 4 (50.0), Cohort 2: 6 (75.0) Total 10: (62.5) Cohort 1 n, (%)/Cohort 2 n, (%)/Total n, (%) Dizziness 0, (0)/3, (37.5)/3, (18.8) Headache 1, (12.5)/2, (25.0)/3, (18.8) Pyrexia 1, (12.5)/2, (25.0)/3, (18.8) Vomiting 2, (25.0)/0, (0)/2, (12.5) Nasopharyngitis 1, (12.5)/1, (12.5)/2, (12.5) Upper abdominal pain 0, (0)/1, (12.5)/1, (6.3) Stomach discomfort 1, (12.5)/0, (0)/1, (6.3) Tinea infection 1, (12.5)/0, (0)/1, (6.3) Upper respiratory tract infection 0, (0)/1, (12.5)/1, (6.3) Enuresis 1, (12.5)/0, (0)/1, (6.3) Cough 0, (0)/1, (12.5)/1, (6.3) Nasal congestion 0, (0)/1, (12.5)/1, (6.3) Sinus congestion 0, (0)/,1 (12.5)/1, (6.3)	The 20 mg/d memantine dose was associated with a higher rate of completion and larger mean improvement on the ADHD-IV and CGI-S than the 10 mg/d memantine dose. Memantine was well tolerated, with most adverse events occurring during the titration phase of the study and rated as mild in severity, with no discontinuations due to adverse events.	Initially, memantine at 10 mg/d (Cohort 1) showed inadequate efficacy and a high dropout rate. Subsequently, an additional 20 mg/d (Cohort 2) was recruited.
Mohammadi et al,[68] 2015, Iran	6-wk, parallel group, randomized clinical trial at Roozbeh Psychiatric Hospital, Tehran	Children and adolescents aged 6–11 with ADHD	*DSM-IV-TR* and K-SADS-PL	ADHD-RS-IV School Version scores 1.5 standard deviations above norms for age and gender	Pervasive developmental disorders, schizophrenia, psychiatric comorbidity requiring pharmacotherapy, suicide risk, mental retardation (IQ < 70), significant chronic medical condition	6 wk	Total 40 (34/6) Memantine 22 (20/2) Methylphenidate 18 (14/4)	Memantine 9.09 ± 1.94 Methylphenidate 8 ± 1.32	Memantine 10–20 mg/d (group 1) or methylphenidate at a dose of 20–30 mg/d depending on weight (20 mg/d for <30 kg and 30 mg/d for >30 kg (group 2) Memantine titrated on following schedule: Week 1: 10 mg/d Week 2: 20 mg/d Methylphenidate titrated on following schedule: Week 1: 10 mg/d Week 2: 20 mg/d Week 3: 30 mg/day for children >30 kg	Parent ADHD Rating Scale, inattention, score ± SD Memantine/methylphenidate Baseline 14.9 ± 3.3/17.1 ± 4.2 Week 3 13.5 ± 5.1/11 ± 3.5 Week 6 13.9 ± 4.8/10.8 ± 4.4 Parent ADHD Rating Scale, hyperactivity/impulsivity Baseline 14.9 ± 5.1/14.5 ± 5.1 Week 3 13 ± 6.9/12.05 ± 5.8 Week 6 12.3 ± 6.03/10.9 ± 4.2 CGI-S Scale at week 6 compared with baseline in the 2 groups $t = 3.05$; $df = 38$; $P = .04$	Methylphenidate (n), memantine (n), *P* Abdominal pain 0, 1, 1.0000 Appetite loss 5, 6, 1.0000 Emotional liability 1, 1, 1.0000 Irritability 7, 3, .1401 Restlessness 4, 2, .3810 Fatigue 2, 3, 1.0000 Headache 1, 3, .6133 Sadness 1, 0, .4500 Trouble sleeping 2, 1, .5976 Tic 1, 1, 1.0000 Vomiting 2, 3, 1.0000 Nausea 2, 3, 1.0000	Memantine can be considered as an alternative treatment for ADHD, although it was less effective than methylphenidate	
Riahi et al,[69] 2020, Iran	Double-blind clinical trial at Golestan Hospital, Ahvaz Jundishapur University of Medical Sciences, Ahvaz, Iran	Children with ADHD aged 6–12 y old	*DSM-5*	Children aged 6–12 y with ADHD based on *DSM-5* and Conners Parent Questionnaire ≥20	Serious psychiatric disorder, seizure, cardiovascular problems, diabetes, allergy to memantine, severe side effects to memantine or methylphenidate	6 wk	Low-dose memantine group: 36 → 16 High-dose memantine group: 36 → 23 Completed treatment: 39 (34/5)	Low-dose memantine group: 7.79 ± 2.15 High-dose memantine group: 10.57 ± 1.67	Low-dose group: 0.1 mg/kg of memantine + methylphenidate High-dose group: 0.25–0.5 mg/kg of memantine + methylphenidate	Conners Parent Questionnaire Score, N, Mean, (Min, Max), SD, *P* Baseline Low-dose group: 16, 23.38 (20, 28), 2.45 High-dose group: 23, 24.17 (17, 31), 2.76 *P* = .275 Week 2 Low-dose group: 16, 19 (14, 25), 3.20 High-dose group: 23, 18.78, (13, 24), 2.913 –*P* = .921 Week 4 Low-dose group: 16, 15.69 (11, 22), 3.14 High-dose group: 23, 15.22, (10, 21), 2.91 *P* = .7 Week 6 Low-dose group: 16, 12.69, (8, 18), 3.07 High-dose group: 23, 12.52, (7, 19), 2.84 *P* = .966	5 patients were excluded due to adverse effects (2 from the low-dose group and 3 from the high-dose group)	Memantine was effective in reducing ADHD symptoms; no significant benefit of higher dose over lower dose; recommend lower dose to minimize side effects	The gender distribution and types of adverse effects among study participants are not specified.
Studies about adult patients with ADHD													
Surman et al,[72] 2013, US	Open-label, prospective study at Massachusetts General Hospital	Adults aged 18–60 with ADHD or ADHD NOS	*DSM-IV* with structured interview	Diagnosis of ADHD or ADHD NOS, score ≥14 on AISRS inattentive items, and CGI-S ADHD score of 4 or higher	Renal/hepatic impairment, organic brain disorder, seizure disorder, IQ ≤75, unstable psychiatric conditions, substance dependence/abuse within 6 mo, pregnant/nursing, hypersensitivity to memantine	12 wk	34 (25/9)	41.8 (18–60, min-max)	Memantine was initiated at 5 mg in the morning at the baseline visit and increased as tolerated to 5 mg twice a day (BID) at week 1–10 mg in the morning and 5 mg later in the day at week 2, and to 10 mg BID at week 3	AISRS change of score, [95% CI], *P* ADHD total symptoms At week 6–15.5, [−11.1, −19.8], *P* < .001 At week 12 −17.5, [−12.6, −22.3], *P* < .001 Inattentive symptoms At week 6 −9.9, [−7.0, −12.8], *P* < .001; At week 12 −10.6, [−7.5, −13.7], *P* < .001 Hyperactive symptoms At week 6 −5.6, [−3.7, −7.4], *P* < .001 At week 12 −6.9, [−4.7, −9.0], *P* = .002 BRIEF-A All subscales of the BRIEF-A, which measures executive function, showed significant improvement from baseline to end point. Cognitive performance by CANTAB Improvements were observed in measures of attention, working memory, and other executive domains by weeks 6 and 12, with *P* < .05.	Number of subjects with 1 adverse event during the trial, N, (%) Dizzy/lightheaded 8, (24) Gastrointestinal 6, (18) Musculoskeletal 6, (18) Headache 5, (15) Sedation 4, (12) Decreased energy 3, (9) Anxiety 2, (6) Cold/infection/allergy 2, (6) Hearing change 2, (6) Impaired concentration 2, (6) Insomnia 2, (6) Asthma 1, (3) Change in sexual function 1, (3) Decreased appetite 1, (3) Increased energy 1, (3) Injury 1, (3) Mucosal dryness 1, (3) Palpitation 1, (3) Tense/jittery 1, (3) Vision/ocular 1, (3)	Memantine was well-tolerated and associated with improvement in ADHD symptoms and cognitive performance; randomized studies are recommended.	An open-label pilot study by Biederman et al, 2017, conducted by the same research team.
Biederman et al,[70] 2017, US	12-wk, double-blind, placebo-controlled, randomized clinical trial with open-label stimulant pharmacotherapy	Adults aged 18–57 with ADHD and executive function deficits (EFDs)	*DSM-IV*	Full *DSM-IV* ADHD criteria, AISRS score ≥20, T-score ≥65 on at least 2 BRIEF-A subscales	IQ < 80, unstable psychiatric condition, history of nonresponse or intolerance to stimulant-class medications or memantine, depression or anxiety unless had been stabilized for at least 2 mo on an SSRI	12 wk	Memantine + stimulant group: 12 (5/7) Stimulant-only group: 14 (7/7)	Memantine + stimulant group: 34.3 ± 9.8 Stimulant-only group: 36.2 ± 10.9	Memantine group: start 5 mg QD to 10 mg BID by week 3 OROS-MPH is prescribed openly, beginning at 36 mg/d, and titrated to optimal response up to a maximum of 1.3 mg/kg or 108 mg/d by clinician judgment	AISRS SMD = −0.29; 95% CI, [−1.07, 0.48]; *P* = .67 BRIEF-A-GEC SMD = 0.02; 95% CI, [−0.79, 0.84]; *P* = .95 Memantine group showed improvement on BRIEF-A individual scale SMD ≥0.5 Inhibition scale SMD = 1.07; 95% CI, [−0.24, 2.32] Self-monitor scale SMD = 0.56; 95% CI, [−1.21, 2.27] Stimulant-only group showed improvement in SMD ≥0.5 Organization of materials scale SMD = −0.71; 95% CI, [−1.74, 0.35] Memantine group showed improvement on the BRIEF-A-GEC scale 50% vs 20%, *P* < .05 More memantine participants (OR > 3) than placebo participants normalized their abnormal baseline BRIEF-A scales (5/12 vs 2/12).	Stimulant only group 1 of 14, 7.1%; reported hand twitching Memantine + OROS-MPH group 2 of 12, 16.6%; reported hand twitching 1 increased anxiety and lightheadedness 1 increased anxiety and changes in vision Memantine group/placebo group, n, (%) Any event 10, (83.3)/13, (92.9) Alcohol intolerance 2, (16.7)/0, (0.0) Anxiety 2, (16.7)/2, (14.3) Appetite decrease 5, (41.7)/1, (7.1) Chest discomfort 0, (0.0)/2, (14.3) Dizziness 2, (16.7)/0, (0.0) Dry mouth 6, (50.0)/6, (42.9) Fatigue 4, (33.3)/3, (21.4) Forgetting 1, (8.3)/2, (14.3) Head discomfort 1, (8.3)/3, (21.4) Headache 6, (50.0)/2, (14.3) Insomnia 3, (25.0)/6, (42.9) Irritable 2, (16.7)/2, (14.3) Jittery 2, (16.7)/4, (28.6) Lightheaded feeling 2, (16.7)/0, (0.0) Nausea 2, (16.7)/1, (7.1) Palpitations 4, (33.3)/3, (21.4) Perceptual change 2, (16.7)/0, (0.0) Sweaty palms 2, (16.7)/0, (0.0)	Memantine might improve behavioral manifestations of EFDs in ADHD, warranting further research.	Only 1 participant on stable dextroamphetamine for more than 2 y entered the study; other participants began OROS-methylphenidate at baseline. One memantine group participant had a stable, years-long history of SSRI use (escitalopram) before enrollment.
Mohammadzadeh et al,[71] 2019, Iran	Randomized, double-blind, placebo-controlled trial at Kurdistan University of Medical Sciences, Sanandaj, Iran	Adult patients with ADHD aged 18–45 y	*DSM-IV-TR* criteria, Conners screening questionnaire, K-SADS-PL for childhood ADHD	Age 18–45, not on medication affecting mental status for 2 wk prior, confirmation of childhood ADHD by clinical interview and K-SADS-PL	Mental disability, other psychiatric disorders, substance/alcohol abuse, pregnancy, allergy to memantine, serious medical illness, uncontrolled seizures, specific blood pressure/pulse rates	6 weeks	Memantine group: 20 (3/17) Placebo group: 20 (3/17)	Memantine group: 34.7 ± 4.48 Placebo group: 31.5 ± 7.4	Memantine or placebo: 10 mg 1 tablet for week 1, 10 mg 2 tablets after week 2	Memantine/placebo, mean ± SD CAARS-S:S Inattention/memory problems $f = 14.07$, $P \leq .001$ Baseline: 1.8 ± 11.8/12.2 ± 1.6 Week 3: 2.7 ± 9.2/11.8 ± 2.1 Week 6: 7.6 ± 3/12.4 ± 1.5 Hyperactivity/restlessness $F = 14$, $P \leq .001$ Baseline: 7 ± 3.5/11.4 ± 1.8 Week 3: 9.05 ± 2.6/11.5 ± 2.2 Week 6: 12.6 ± 1.5/11.8 ± 1.5 Impulsivity/emotional lability $f = 14$, $P \leq .001$ Baseline: 9.6 ± 2.4/9.9 ± 2.3 Week 3: 8 ± 2.5/9.8 ± 2.6 Week 6: 6.2 ± 3.4/10.3 ± 2.7 Problems with self-concept $f = 4$, $P \leq .001$ Baseline: 7 ± 2.1/12.4 ± 1.8 Week 3: 7.7 ± 2.9/11.7 ± 2.4 Week 6: 9 ± 2.9 11.6 ± 2.4 ADHD Index $f = 24$, $P \leq .001$ Baseline: 56.4 ± 5.1/59.3 ± 5.4 Week 3: 43.9 ± 9.1/57.2 ± 8.5 Week 6: 36.7 ± 12.9/59.7 ± 6.2	Memantine was well tolerated, and severe side effects were not observed, but mild to moderate side effects were common, and the medication was discontinued in 6 patients.	Memantine is effective in reducing symptoms of ADHD in adults and has tolerable side effects.	The participants of this study were parents whose children were diagnosed with ADHD before enrollment.

Abbreviations: ADHD-RS-IV = ADHD Rating Scale, fourth edition, ADHD-RS-IV-:I = ADHD Rating Scale, fourth edition-inattentive domain, ADHD-RS-IV-H = ADHD Rating Scale, fourth edition-hyperactive/impulsive domain, AISRS = Adult ADHD Investigator Symptom Rating Scale, BRIEF-A = Behavior Rating Inventory of Executive Functions-Adults, BRIEF-A-GEC = Behavior Rating Inventory of Executive Functions-Adults-Global Executive Composite, CGI-S = Clinical Global Impressions-Severity, CAARS-S:S = Conners Adult ADHD Rating Scale-Short Self-Report, *DSM-IV-TR* = Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition, Text Revision, *DSM-5* = Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition, K-SADS-PL = Kiddie Schedule for Affective Disorders and Schizophrenia for School-Aged Children–Present and Lifetime Version, SMD = standardized mean difference, TEAE = treatment-emergent adverse events.