Title

Amantadine for the treatment of childhood and adolescent psychiatric symptoms

Journal

Baylor University Medical Center Proceedings, 34(5)

ISSN

0899-8280

Authors

Morrow, Kyle
Choi, Sun
Young, Keith
et al.

Publication Date

2021-09-03

DOI

10.1080/08998280.2021.1925827

Peer reviewed

PROC (BAYL UNIV MED CENT)
2021;34(5):566–570

https://doi.org/10.1080/08998280.2021.1925827

Taylor & Francis
Taylor & Francis Group

Amantadine for the treatment of childhood and adolescent psychiatric symptoms

Kyle Morrow, MD[a,b], Sun Choi, BA[a,b], Keith Young, PhD[a,b], Makram Haidar, MD[a,b], Cassandra Boduch, MD[a,b], and James A. Bourgeois, OD, MD[a,b]

Department of Psychiatry, Baylor Scott & White Health, Temple, Texas; Texas A&M University College of Medicine, Temple, Texas

ABSTRACT

This retrospective study examined clinical parameters associated with amantadine treatment of psychiatric symptoms in children. A total of 297 pediatric patients were prescribed amantadine and met study criteria to assess clinical responses and medication outcomes. More than 62% of patients experienced clinically significant symptom control and 83% achieved at least maintenance symptom control, while 11% discontinued amantadine for nonresponse and 6% stopped amantadine because of side effects. Among patients previously receiving other psychotropic medication, 42% and 28% of patients fully discontinued second- or third-generation antipsychotics or antidepressants, respectively. Patients responsive to amantadine who discontinued or reduced antipsychotic dose experienced a significant reduction in body mass index. Amantadine appears be an efficacious and safe alternative for treatment of a broad set of psychiatric symptoms in children and adolescents. Specifically, it may serve as an effective adjunct to stimulants for attention deficit/hyperactivity disorder–related symptoms and appears to be a safer alternative to second- or third-generation antipsychotics.

KEYWORDS Amantadine; attention-deficit hyperactivity disorder; child and adolescent psychiatry; major depressive disorder; psychotropic medications

Amantadine hydrochloride, an indirect dopamine agonist and N-methyl-D-aspartate receptor antagonist, can modulate symptoms of childhood psychiatric disorders.[1–4] Multiple studies have reported effective off-label use of amantadine in attention deficit/hyperactivity disorder (ADHD) and as an augmenting agent in treatment-resistant unipolar depression, autism spectrum disorder, and obsessive-compulsive disorder.[5–13] Common side effects of amantadine include nausea, dizziness, and insomnia.[14] Rare side effects include psychosis, hypertension, livedo reticularis, and rash.[15] Stimulants and nonstimulants used to treat ADHD are associated with more severe side effects, while antipsychotics have been associated with weight gain, extrapyramidal symptoms, QTc prolongation, and sedation.[16,17] Some studies report that amantadine can reverse weight gain induced by antipsychotics.[18–23] This study was a retrospective chart review of children and adolescents prescribed amantadine to assess its tolerability and treatment outcomes for psychiatric symptoms.

METHODS

We conducted a retrospective cohort study at the Baylor Scott & White Pediatric Mental Health Clinic in Temple, Texas, to establish the proportion of successful treatments compared to failures as well as the proportion of patients who were able to reduce or transition off their existing psychotropic medications. Eligible patients were defined as any patients aged 5 to 18 years who were prescribed amantadine by a psychiatrist.

We accessed child psychiatry outpatient charts in the Epic electronic medical record from February 1, 2014, to February 1, 2018, and extracted data on age, sex, ethnicity, body mass index (BMI), weight percentile, duration of psychotropic treatment, dosage of amantadine response, clinical psychiatric diagnoses, target symptoms, clinic notes, other medication history, medications decreased in dose and/or discontinued after initiation of amantadine, and side effects attributed to amantadine. Comorbidities were recorded for each patient, including diagnoses of ADHD, depressive and

Corresponding author: James A. Bourgeois, OD, MD, Department of Psychiatry, Baylor Scott & White Health, 2401 South 31st Street, Temple, TX 76508 (e-mail: james.bourgeois@bswhealth.org)

The authors report no conflicts of interest.

Received March 21, 2021; Revised April 23, 2021; Accepted April 26, 2021.

Table 1. Treatment outcomes of amantadine in children and adolescents, overall and by diagnosis

Diagnosis	Total	Success	Minimal	Failure	SE D/C
Full study group	297	185 (62.3%)	61 (20.5%)	34 (11.4%)	17 (5.7%)
ADHD	251	162 (64.5%)	52 (20.7%)	27 (10.8%)	10 (4.0%)
ODD/CD	190	114 (60%)	43 (22.6%)	19 (10%)	14 (7.4%)
Depressive disorder	36	24 (66.7%)	10 (27.8%)	2 (5.6%)	0
Anxiety disorder/OCD	92	62 (67.4%)	17 (18.5%)	9 (9.8%)	4 (4.4%)
Autistic spectrum disorder	59	40 (67.8%)	12 (20.3%)	2 (3.4%)	5 (8.5%)
PTSD	18	10 (55.6%)	2 (11.1%)	6 (33.3%)	0
Intellectual disability	43	28 (65.1%)	10 (23.3%)	4 (9.3%)	1 (2.3%)

ADHD indicates attention deficit/hyperactivity disorder (combined and inattentive); OCD, obsessive-compulsive disorder; ODD/CD, oppositional defiant disorder/conduct disorder; PTSD, posttraumatic stress disorder; SE D/C, side effect discontinuation.

anxiety disorders, oppositional defiant disorder, conduct disorder, posttraumatic stress disorder, obsessive compulsive disorder, and autism.

We classified clinical responses to amantadine as "success" or "partial success" based on clinician-reported assessment of patient psychiatry status over a minimum of 3 months, while all "treatment failure" or "side effect" discontinuations were classified independent of the interval. Chart notation of symptom improvement or abatement or dose decrease without discontinuation was classified as a treatment success. Partial behavioral control, defined as a decreased level of symptom compared to baseline, which warranted the continuation of amantadine, was classified as a partial success. Discontinuation of amantadine due to poor behavioral control was classified as treatment failure. Discontinuation due to side effects was classified as a side effect discontinuation. Patients were further classified as having their original doses of antipsychotics, stimulants, and antidepressants reduced by >50% or discontinued completely after starting amantadine. For patients originally taking second- or third-generation antipsychotics, BMI was calculated at the initial appointment when amantadine was prescribed and then after 1 year of amantadine treatment.

A total of 297 patients newly prescribed amantadine with available data during the 48-month look-back window were included in the database. Data analysis was performed using descriptive statistics and one-way analysis of variance with post hoc testing.

RESULTS

Of the 297 patients who ranged from 6 to 18 years and were diagnosed with a variety of psychiatric illnesses (ADHD being the most common), 62.3% achieved treatment success and 20.5% achieved partial success after >3 months of new prescriptions of amantadine *(Table 1)*. Among patients who achieved partial or full therapeutic responses, 91.1% (224/246) continued amantadine therapy for at least 6 months and 79.7% (196/246) continued for 1 year. Many patients who achieved treatment success continued amantadine therapy beyond the review interval. Regarding nonresponse and discontinuation, 11.4% (34/297) of patients failed to achieve any symptom relief and 5.7% (17/297) experienced side effects that led to discontinuation of amantadine. The most common side effects noted for discontinuation were irritability, anxiety, gastrointestinal/weight loss, and sedation.

For treatment success, the median dose of amantadine was 200 mg daily; 13 patients needed 100 mg daily or less, whereas 12 patients needed as much as 400 mg daily. Most patients had multiple psychiatric comorbidities, with ADHD and oppositional defiant disorder/conduct disorder being the most common *(Table 2)*. Amantadine success and partial success rates were similar across all diagnoses. Except for posttraumatic stress disorder (6 out of 18 failures, 33%), failure rates were also similar across all diagnoses *(Table 1)*.

Eight out of 184 patients who were considered a treatment success were able to eventually discontinue amantadine because symptoms improved to the point that amantadine and any other psychotropic medications were no longer necessary. Clinician follow-up during the study interval found no indication that their symptoms relapsed, and neither amantadine nor any other psychotropic medication was restarted. No study patients were diagnosed with bipolar disorder because clinicians were aware of prior reports describing a switch to mania after amantadine initiation.[24,25]

We studied several specific symptom clusters across all diagnosis groups *(Table 3)*. Amantadine treatment was most efficacious with impulsivity symptoms, with over 70% of patients reporting symptom improvement. Irritability/anger saw the next greatest improvement, at over 50%.

We found that 114 of 297 patients (38.4%) completely discontinued or decreased the dosage by >50% of their existing psychotropic prescriptions after a successful or partially successful response to amantadine. Of the patients previously prescribed second- or third-generation antipsychotics who

Table 2. Comorbidities by psychiatric diagnosis for patients taking amantadine

	ADHD	ODD/CD	Depressive disorder	Anxiety/OCD	Autistic disorder	PTSD	ID
ADHD (n = 251)	–	160 (64%)	33 (13%)	82 (33%)	44 (18%)	15 (6%)	34 (14%)
ODD/CD (n = 190)	160 (84%)	–	25 (13%)	61 (24%)	22 (12%)	8 (4%)	24 (13%)
Depressive disorder (n = 36)	33 (92%)	25 (69%)	–	10 (28%)	2 (6%)	1 (3%)	4 (11%)
Anxiety/OCD (n = 92)	82 (89%)	61 (66%)	10 (11%)	–	11 (12%)	3 (3%)	12 (13%)
Autistic disorder (n = 59)	44 (75%)	22 (37%)	2 (3%)	11 (19%)	–	1 (2%)	11 (19%)
PTSD (n = 18)	15 (83%)	8 (44%)	1 (6%)	3 (17%)	1 (6%)	–	4 (22%)
ID (n = 43)	34 (79%)	24 (56%)	4 (9%)	12 (28%)	11 (26%)	4 (9%)	–

ADHD indicates attention deficit/hyperactivity disorder; ID, intellectual disability; OCD, obsessive-compulsive disorder; ODD/CD, oppositional defiant disorder/conduct disorder; PTSD, posttraumatic stress disorder.

Table 3. Reported symptom improvement by psychiatric diagnosis after amantadine

Diagnosis	Impulsivity	Irritability/anger	Focus/concentration	Aggression/outbursts	Thought processing
ADHD (n = 214)	176 (82%)	112 (52%)	109 (51%)	63 (29%)	44 (21%)
ODD/CD (n = 157)	130 (83%)	85 (54%)	69 (44%)	47 (30%)	31 (20%)
Depressive disorder (n = 34)	25 (74%)	18 (53%)	12 (35%)	17 (50%)	4 (12%)
Anxiety disorder/OCD (n = 79)	65 (82%)	44 (56%)	29 (37%)	13 (16%)	24 (30%)
ASD (n = 52)	41 (79%)	29 (56%)	28 (54%)	7 (13%)	10 (19%)
PTSD (n = 12)	10 (83%)	6 (50%)	7 (58%)	1 (8%)	4 (33%)
Intellectual disability (n = 38)	32 (84%)	20 (53%)	10 (26%)	10 (26%)	10 (26%)

ADHD indicates attention deficit/hyperactivity disorder; ASD, autism spectrum disorder; OCD, obsessive-compulsive disorder; ODD/CD, oppositional defiant disorder/conduct disorder; PTSD, posttraumatic stress disorder.

had successful or partial response to amantadine, 38 out of 83 (45.8%) were able to completely discontinue or reduce (aripiprazole being the most common). Patients taking nonstimulant medication (e.g., atomoxetine, guanfacine) approved for ADHD discontinued or reduced doses at a much higher rate (44.9%) compared to the discontinuation rate (19.2%) of stimulant medication (e.g., methylphenidate, amphetamine). Of note, 103 of 214 patients (48.1%) diagnosed with ADHD who responded to amantadine received combination therapy with a stimulant. Patients who had previously failed a Food and Drug Administration (FDA)–approved medication had good outcomes with amantadine; 63 of 72 patients (87.5%) who had failed stimulants and 56 of 62 (90.3%) who had failed guanfacine or atomoxetine achieved treatment success or partial success. Twenty-one of 75 patients (28.0%) were able to discontinue their selective serotonin reuptake inhibitor antidepressant medication.

Amantadine treatment responders experienced statistically significant improvements in BMI 1 year after antipsychotic reduction or discontinuation (4.5% reduction, $P < 0.027$) *(Figure 1)*. Treatment responders remaining on antipsychotics experienced a mean 4% increase in BMI over this interval. The difference between remaining on or discontinuing antipsychotics for 1 year was on average thus close to 8% of total BMI, a substantial reduction. The BMI reduction for many patients started early after antipsychotic discontinuation or reduction, with 22 of 29 (75.9%) experiencing a net decrease in BMI and 13 of 29 (44.8%) experiencing a >5% decrease after 6 months.

DISCUSSION

The primary goals of this study were to report on amantadine's utility and tolerability in child and adolescent psychiatric patients. A large majority reported at least partial symptom improvement on amantadine. Amantadine was most effective in decreasing symptoms of impulsivity, irritability, and anger and improving focus/concentration. Amantadine was well tolerated, with less than 6% discontinuing due to side effects. Most patients continued amantadine therapy for more than a year and <12% of patients discontinued amantadine due to lack of response. The median daily dose was 200 mg per day.[15]

Only 19% of patients were able to fully discontinue stimulant use, providing support for previous reports that amantadine is not as efficacious as stimulants in children

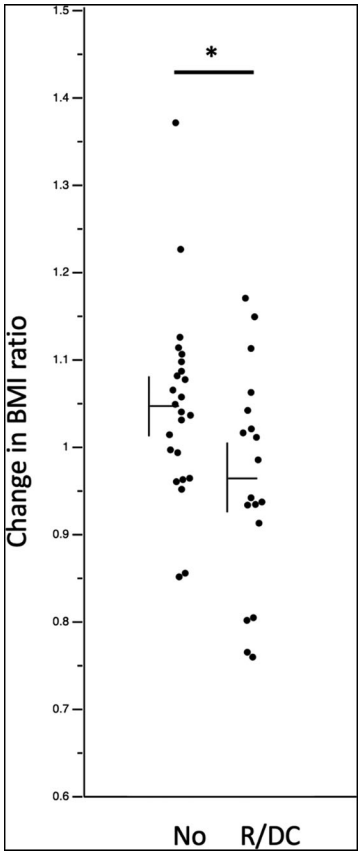

Figure 1. Effect of atypical antipsychotic dose reduction on body mass index (BMI). Doses of second- or third-generation antipsychotics were either not reduced (No) or reduced by 50% to 100% (R/DC) after initiating amantadine. BMI was calculated at the initial date of amantadine prescription and then at 12 months. *t test indicates antipsychotic reduction or discontinuation improved BMI over a 12-month interval ($t = 2.30$, $P < 0.027$).

with ADHD.[7,8] Rather, the utility of amantadine in ADHD patients may be as an *adjunct* to stimulants or as a third-line therapeutic, with over 88% of patients who had previously failed FDA-approved ADHD medication achieving at least maintenance symptom control. Almost half of the patients who successfully responded to amantadine were able to continue a stimulant at lower doses.

Clinicians often utilize antipsychotics off-label for many child psychiatric conditions.[26] These treatments have concerning side effects, including dyslipidemia, metabolic disorders, weight gain, and diabetes mellitus.[27–31] We found that amantadine use in children who were previously prescribed antipsychotics allowed many of them (46%) to either completely discontinue or decrease dosages of antipsychotic by >50%. After 1 year of antipsychotic reduction or discontinuation, there was a statistically significant decrease in BMI, whereas those who did *not* decrease or discontinue antipsychotics had an *increase* in BMI. Previously, our group found oxcarbazepine to be effective in treating child psychiatric symptoms, with similar utility for reducing BMI in patients who were able to reduce dose or discontinue antipsychotics.[32]

The limitations of the present study are its nonrandomized, nonblinded design and data collection method based on clinician-reported assessments of symptoms. However, the findings are based on a large set of cases involving a wide range of psychiatric conditions treated in an academic medical center–based child health care system.

Overall, our study provides additional evidence demonstrating amantadine's effectiveness in child psychiatry. Clinicians should consider amantadine as a useful off-label alternative for many psychiatric illnesses. Controlled clinical trials with large study populations comparing amantadine head-to-head to stimulants and antipsychotics are needed.

ORCID

James A. Bourgeois http://orcid.org/0000-0002-1426-474X

1. Fiore AE, Fry A, Shay D, et al. Antiviral agents for the treatment and chemoprophylaxis of influenza—recommendations of the Advisory Committee on Immunization Practices (ACIP). *MMWR Recomm Rep*. 2011;60(1):1–24.
2. King BH, Au D, Poland RE. Pretreatment with MK-801 inhibits pemoline-induced self-biting behavior in prepubertal rats. *Dev Neurosci*. 1995;17(1):47–52. doi:10.1159/000111272.
3. Faraone SV. The pharmacology of amphetamine and methylphenidate: relevance to the neurobiology of attention-deficit/hyperactivity disorder and other psychiatric comorbidities. *Neurosci Biobehav Rev*. 2018;87:255–270. doi:10.1016/j.neubiorev.2018.02.001.
4. Green LB, Hornyak JE, Hurvitz EA. Amantadine in pediatric patients with traumatic brain injury: a retrospective, case-controlled study. *Am J Phys Med Rehabil*. 2004;83(12):893–897. doi:10.1097/01.PHM.0000143400.15346.C8.
5. Hosenbocus S, Chahal R. Amantadine: a review of use in child and adolescent psychiatry. *J Can Acad Child Adolesc Psychiatry*. 2013;22(1):55–60.
6. Masters KJ. Alternative medications for ADHD. *J Am Acad Child Adolesc Psychiatry*. 1997;36(3):301–302. doi:10.1097/00004583-199703000-00001.
7. Mattes J. A pilot trial of amantadine in hyperactive children. *Psychopharmacol Bull*. 1980;16(3):67–69.
8. Donfrancesco R, Calderoni D, Vitiello B. Open-label amantadine in children with attention-deficit/hyperactivity disorder. *J Child Adolesc Psychopharmacol*. 2007;17(5):657–664. doi:10.1089/cap.2006.0128.
9. Mohammadi MR, Kazemi MR, Ebtahal Z, et al. Amantadine versus methylphenidate in children and adolescents with attention deficit/hyperactivity disorder: a randomized, double-blind trial. *Hum Psychopharmacol*. 2010;25(7-8):560–565. doi:10.1002/hup.1154.
10. Stryjer R, Strous RD, Shaked G, et al. Amantadine as augmentation therapy in the management of treatment-resistant depression. *Int Clin Psychopharmacol*. 2003;18(2):93–96. doi:10.1097/00004850-200303000-00005.
11. Rogoz Z, Skuza G, Daniel W, et al. Amantadine as an additive treatment in patients suffering from drug-resistant unipolar depression. *Pharmacol Rep*. 2007;59(6):778–784.
12. Pasquini M, Berardelli I, Biondi M. Amantadine augmentation for refractory obsessive-compulsive disorder: a case report. *J Clin Psychopharmacol*. 2010;30(1):85–86. doi:10.1097/JCP.0b013e3181c8b44f.
13. King BH, Wright DM, Handen BL, et al. Double-blind, placebo-controlled study of amantadine hydrochloride in the treatment of children with autistic disorder. *J Am Acad Child Adolesc Psychiatry*. 2001;40(6):658–665. doi:10.1097/00004583-200106000-00010.

14. Raupp-Barcaro IF, Vital MA, Galduróz JC, et al. Potential antidepressant effect of amantadine: a review of preclinical studies and clinical trials. *Braz J Psychiatry*. 2018;40(4):449–458. doi:10.1590/1516-4446-2017-2393.
15. Endo Pharmaceuticals Inc Symmetrel (Amantadine). 2007 [accessed March 17, 2021]. https://www.accessdata.fda.gov/drugsatfda_docs/label/2009/016023s041,018101s016lbl.pdf.
16. Wolraich ML, Hagan JF Jr, Allan C, et al. Clinical practice guideline for the diagnosis, evaluation, and treatment of attention-deficit/hyperactivity disorder in children and adolescents. *Pediatrics*. 2019;144(4):e20192528. doi:10.1542/peds.2019-2528.
17. Sultan RS, Wang S, Crystal S, Olfson M. Antipsychotic treatment among youths with attention-deficit/hyperactivity disorder. *JAMA Netw Open*. 2019;2(7):e197850. doi:10.1001/jamanetworkopen.2019.7850.
18. Gracious BL, Krysiak TE, Youngstrom EA. Amantadine treatment of psychotropic-induced weight gain in children and adolescents: case series. *J Child Adolesc Psychopharmacol*. 2002;12(3):249–257. doi:10.1089/104454602760386941.
19. Correa N, Opler L, Kay S, et al. Amantadine in the treatment of neuroendocrine side effects of neuroleptics. *J Clin Psychopharmacol*. 1987;7(2):91–95.
20. Floris M, Lejeune J, Deberdt W. Effect of amantadine on weight gain during olanzapine treatment. *Eur Neuropsychopharmacol*. 2001;11(2):181–182. doi:10.1016/S0924-977X(01)00072-4.
21. Graham KA, Gu H, Lieberman JA, et al. Double-blind, placebo-controlled investigation of amantadine for weight loss in subjects who gained weight with olanzapine. *Am J Psychiatry*. 2005;162(9):1744–1746. doi:10.1176/appi.ajp.162.9.1744.
22. Bahk WM, Lee KU, Chae JH, et al. Open label study of the effect of amantadine on weight gain induced by olanzapine. *Psychiatry Clin Neurosci*. 2004;58(2):163–167. doi:10.1111/j.1440-1819.2003.01211.x.
23. Maayan L, Vakhrusheva J, Correll CU. Effectiveness of medications used to attenuate antipsychotic-related weight gain and metabolic abnormalities: a systematic review and meta-analysis. *Neuropsychopharmacology*. 2010;35(7):1520–1530. doi:10.1038/npp.2010.21.
24. Sodré LA, Bücker J, Zortéa K, et al. Mania switch induced by amantadine in bipolar disorder: report of three cases. *Braz J Psychiatry*. 2010;32(4):467–469. doi:10.1590/s1516-44462010000400029.
25. Rego MD, Giller EL Jr. Mania secondary to amantadine treatment of neuroleptic-induced hyperprolactinemia. *J Clin Psychiatry*. 1989;50(4):143–144.
26. Brophy S, Kennedy J, Fernandez-Gutierrez F, et al. Characteristics of children prescribed antipsychotics: analysis of routinely collected data. *J Child Adolesc Psychopharmacol*. 2018;28(3):180–191. doi:10.1089/cap.2017.0003.
27. Toren P, Ratner S, Laor N, et al. Benefit-risk assessment of atypical antipsychotics in the treatment of schizophrenia and comorbid disorders in children and adolescents. *Drug Saf*. 2004;27(14):1135–1156. doi:10.2165/00002018-200427140-00005.
28. Barker MK, Sable CM, Montgomery SE, et al. Diet and cardiometabolic side effects in children treated with second-generation antipsychotics. *Clin Nutr Espen*. 2018; 23:205–211. doi:10.1016/j.clnesp.2017.09.013.
29. Sjo CP, Stenstrøm AD, Bojesen AB, et al. Development of metabolic syndrome in drug-naive adolescents after 12 months of second-generation antipsychotic treatment. *J Child Adolesc Psychopharmacol*. 2017;27(10):884–891. doi:10.1089/cap.2016.0171.
30. Scahill L, Jeon S, Boorin SJ, et al. Weight gain and metabolic consequences of risperidone in young children with autism spectrum disorder. *J Am Acad Child Adolesc Psychiatry*. 2016;55(5):415–423. doi:10.1016/j.jaac.2016.02.016.
31. Burghardt KJ, Seyoum B, Mallisho A, et al. Atypical antipsychotics, insulin resistance and weight; a meta-analysis of healthy volunteer studies. *Prog Neuropsychopharmacol Biol Psychiatry*. 2018;83:55–63. doi:10.1016/j.pnpbp.2018.01.004.
32. Morrow K, Young KA, Spencer S, et al. Utility of oxcarbazepine in the treatment of childhood and adolescent psychiatric symptoms. *Proc (Bayl Univ Med Cent)*. 2020;34(1):34–39. doi:10.1080/08998280.2020.1826259.