Title

Utility of oxcarbazepine in the treatment of childhood and adolescent psychiatric symptoms

Journal

Baylor University Medical Center Proceedings, 34(1)

ISSN

0899-8280

Authors

Morrow, Kyle
Young, Keith A
Spencer, Shawn
et al.

Publication Date

2021-01-02

DOI

10.1080/08998280.2020.1826259

Peer reviewed

PROC (BAYL UNIV MED CENT)
2021;34(1):34–39

https://doi.org/10.1080/08998280.2020.1826259

Taylor & Francis
Taylor & Francis Group

Utility of oxcarbazepine in the treatment of childhood and adolescent psychiatric symptoms

Kyle Morrow, MD, Keith A. Young, PhD, Shawn Spencer, DO, Edgar Samuel Medina, MD, Michaela A. Marziale, MD, Alejandro Sanchez, MD candidate, and James A. Bourgeois, OD, MD

Department of Psychiatry, Baylor Scott & White Health, Central Texas Division, and College of Medicine, Texas A&M University Health Science Center, Temple, Texas

ABSTRACT

The primary aims of this study were to determine if oxcarbazepine is a safely tolerated option for treatment of psychiatric symptoms in children and whether its use facilitates dose modification of other psychotropic medications. A retrospective chart review was completed using data extracted from the electronic medical record of a large outpatient child psychiatry clinic. A total of 507 of 740 children prescribed oxcarbazepine for psychiatric indications for 3 months or more had adequate data to assess clinical responses and medication outcomes. Most patients prescribed oxcarbazepine experienced clinically significant control of irritability/anger, mood stabilization, aggressive outbursts, impulsivity, or anxiety, with over 80% achieving at least maintenance symptom control. In all, 51% and 25% fully discontinued second- or third-generation antipsychotic or antidepressant medication, respectively, after starting oxcarbazepine; 8% discontinued oxcarbazepine for nonresponse, while 9% stopped oxcarbazepine because of emergent side effects. In patients fully discontinuing or reducing the second- or third-generation antipsychotic dose by 50% or more, improvements in body mass index were observed. Oxcarbazepine may prove to be an appropriate alternative to antipsychotic and antidepressant medications for treating psychiatric symptoms in children and adolescents. In particular, it may be a more metabolically neutral psychotropic medication.

KEYWORDS Anticonvulsants; antipsychotics; child and adolescent psychiatry; oxcarbazepine

Oxcarbazepine, a dibenzazepine carboxamide derivative of carbamazepine, is a voltage-gated sodium channel anticonvulsant.[1] Common side effects of oxcarbazepine include dizziness, somnolence, syndrome of inappropriate antidiuretic hormone secretion, and nausea.[2–4] Rare cutaneous reactions include maculopapular eruption, Stevens-Johnson syndrome, and toxic epidermal necrolysis, which require discontinuation.[5] Oxcarbazepine was cited as an effective treatment for treatment-resistant focal epilepsy in adults.[6] Oxcarbazepine is also used off label as a psychotropic medication in adults[7–13] and for treatment of epilepsy in children and adolescents.[14–16] Unlike some other anticonvulsants, oxcarbazepine spares cognition and does not aggravate symptoms of co-occurring attention deficit hyperactivity disorder (ADHD) and epilepsy.[17] Oxcarbazepine has been used to treat child and adolescent psychiatric disorders. While recent American Association of Child and Adolescent Psychiatry practice parameters do not include oxcarbazepine as a treatment option for autism spectrum disorder (ASD), oppositional defiant disorder, or depressive disorders, oxcarbazepine has been listed as a fifth-line option for treatment of child and adolescent bipolar disorder.[18–21] Negative findings include a double-blind placebo-controlled trial to treat mania in children, which did not find efficacy for oxcarbazepine in this population.[22] More recently, oxcarbazepine was found to be effective in reducing irritability and agitation in ASD.[23,24] Oxcarbazepine was reported by clinicians to be perceived as one of the best-tolerated treatments for childhood behavioral problems associated with ASD and other conditions.[25] To better document clinical impressions of oxcarbazepine in

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 reported no conflicts of interest or external funding.

Received July 28, 2020; Revised September 15, 2020; Accepted September 17, 2020

Table 1. Overall treatment outcomes of oxcarbazepine in 507 children and adolescents

Outcome	Number	Percent
Treatment success	339	66.9%
Partial success	77	15.2%
Treatment failure	42	8.3%
Side effect discontinuation	49	9.7%

children and adolescents, we performed a retrospective chart review focusing on tolerability and treatment outcomes.

METHODS

We reviewed all new oxcarbazepine prescriptions by Baylor Scott and White Health psychiatrists to pediatric patients over a period of 15 months to determine the proportion of patients who were subsequently able to reduce or transition off their existing alternative psychotropic medication, and to determine changes in body mass index (BMI) after replacing or reducing the dose of second- and third-generation antipsychotics.

Child psychiatry outpatient charts in the Epic electronic medical record from February 1, 2014, to April 30, 2015, were accessed to gather data on age, gender, duration of psychotropic treatment, maintenance dosage of oxcarbazepine, clinical psychiatric chart diagnoses, specific symptoms, other medication history, and medications decreased in dose and/or discontinued after initiation of oxcarbazepine. In this clinical sample, there was a high level of comorbidity. Diagnoses of ADHD, depressive and anxiety disorders, posttraumatic stress disorder (PTSD), oppositional defiant disorder, and autism shared similar symptom concerns of irritability, disruptive behavior, aggression, and mood changes.

Two of the authors (KM, ESM) classified clinician-reported assessment of patient psychiatric status over a minimum of 3 months. Caregiver report of improvement or maintenance of good behavioral control was classified as a treatment success. Partial behavioral control at a reduced level of symptom burden compared to baseline, which was at an acceptable level with continuation of oxcarbazepine, was classified as a partial success. Poor behavioral control leading to subsequent discontinuation of oxcarbazepine was classified as treatment failure. Discontinuation of oxcarbazepine because of side effects was classified as a side effect discontinuation. Each patient was classified as subsequently managed with greater or less than 50% dose reduction from the original dose of psychostimulant, antidepressant, or antipsychotic at the time of oxcarbazepine prescription. For the subset of patients originally taking second- or third-generation antipsychotics, BMI was calculated at the initial appointment before oxcarbazepine was prescribed and then after 6 months of oxcarbazepine treatment.

Descriptive statistics and analysis of variance with post hoc testing were utilized to analyze the data. During the study interval, 736 patients received new prescriptions for oxcarbazepine. Data from 507 patients with at least 3 months of follow-up data and sufficient clinician behavioral descriptions for assessment of clinical response were included in the final data set. All patients who had oxcarbazepine discontinued because of an unacceptable benefit/side effect or lack of efficacy within the initial 3-month window were included in the dataset, even if they did not meet the 3-month treatment duration criterion. Most patients not included in the study were cases for which oxcarbazepine had been prescribed for a seizure disorder. The minority of patients not included were related to either not starting the medication or being lost to follow-up.

RESULTS

The patients ranged in age from 6 to 18 years and were treated for a variety of psychiatric illnesses. Most patients were successfully treated with oxcarbazepine for >3 months and achieved a classification of treatment success (66.9%), with an additional 15.2% classified as a partial success with continuation of oxcarbazepine *(Table 1)*.

Many patients (N = 241/507) with at least partial therapeutic responses were then continued on oxcarbazepine for at least 1 year, while another 129 were maintained for at least 6 months of treatment during the review interval. It should be noted that this is a conservative estimate of treatment duration, as oxcarbazepine was being added throughout the retrospective review interval, and many patients continued oxcarbazepine therapy after the review interval ended. Only 8.3% of the patients did not experience acceptable behavioral control (leading to oxcarbazepine discontinuation), while 9.7% of patients discontinued oxcarbazepine due to an unacceptable benefit/side effect experience. Six out of 212 with available laboratory results displayed transient evidence of hyponatremia, with no patient withdrawn from oxcarbazepine for this issue. Specific side effects noted as contributing to discontinuation included blurry vision, headache, irritability, rash, somnolence, and dizziness.

The median daily dose for effective treatment response was 600 mg/day; dosages exceeded 1200 mg/day in only three cases. Successful therapeutic response and discontinuation rates were similar for all psychiatric diagnoses for which oxcarbazepine was used *(Table 2)*. In 13 cases, oxcarbazepine was withdrawn and not replaced with any alternative prescribed medication due to highly advantageous improvements in behavioral symptoms. There were no indications that symptoms returned in these cases, and neither oxcarbazepine nor other psychotropic medications were restarted during the retrospective assessment interval. Of note, there were no patients with a diagnosis of bipolar disorder, as physicians in the clinic followed the recommendation that oxcarbazepine is not efficacious for bipolar disorder in children and adolescents.

Table 2. Outcomes of oxcarbazepine treatment by psychiatric diagnosis

Diagnosis	Total	Treatment success (n = 339)	Partial success (n = 77)	Treatment failure (n = 42)
ADHD	302	241 (79.8%)	42 (14%)	19 (6%)
ODD	268	192 (71.6%)	49 (18%)	27 (10%)
Depressive disorder	195	146 (74.9%)	34 (17%)	15 (8%)
Anxiety disorder	184	130 (70.7%)	36 (20%)	18 (10%)
Autistic disorder	63	49 (77.8%)	6 (10%)	8 (13%)
PTSD	30	18 (60.0%)	9 (30%)	3 (10%)

ADHD indicates attention-deficit hyperactivity disorder; ODD, oppositional defiant disorder; PTSD, posttraumatic stress disorder.

Table 3. Reported symptom improvement by psychiatric diagnosis after oxcarbazepine treatment

Diagnosis (N)	Irritability/anger	Mood stabilization	Aggressive outbursts	Impulsivity	Sadness/depression	Anxiety/worry
ADHD (283)	276 (98%)	191 (67%)	177 (63%)	60 (21%)	29 (10%)	46 (16%)
ODD (241)	237 (98%)	168 (70%)	159 (66%)	71 (29%)	31 (13%)	44 (18%)
Depression (180)	168 (93%)	140 (78%)	92 (50%)	36 (20%)	42 (23%)	36(20%)
Anxiety disorder (166)	156 (94%)	132 (80%)	91 (55%)	49 (30%)	33 (20%)	69 (42%)
Autistic disorder (55)	52 (95%,)	24 (44%)	42 (76%)	10 (18%)	1 (1.8%)	6 (11%)
PTSD (27)	26 (96%)	18 (67%)	18 (67%)	4 (15%)	5 (19%)	2 (7%)

ADHD indicates attention-deficit hyperactivity disorder; ODD, oppositional defiant disorder; PTSD, posttraumatic stress disorder.

Table 4. Comorbidities by psychiatric diagnosis in 507 children and adolescents treated with oxcarbazepine

Diagnosis (N)	ADHD	ODD	Depression	Anxiety disorder	Autistic disorder	PTSD
ADHD (283)	—	182 (64%)	107 (38%)	96 (34%)	32 (11%)	13(5%)
ODD (241)	182 (76%)	—	85 (35%)	85 (35%)	11 (5%)	11 (5%)
Depression (180)	107 (59%)	85 (47%)	—	77 (43%)	6 (3%)	7 (4%)
Anxiety disorder (166)	96 (58%)	85 (51%)	77 (46%)	—	15 (9%)	4 (2%)
Autistic disorder (55)	32 (58%)	11 (20%)	6 (11%)	15 (27%)	—	0 (0%)
PTSD (32)	13 (41%)	11(34%)	7 (22%)	4 (13%)	0 (0%)	—

ADHD indicates attention-deficit hyperactivity disorder; ODD, oppositional defiant disorder; PTSD, posttraumatic stress disorder.

Regarding specific clinical symptom cluster responses across all psychiatric diagnosis groups, we assessed several specific symptom clusters, as shown in *Table 3*. Improvement in irritability/anger was over 90%, consistent with the hypothesis of anticonvulsants acting through a mechanism of decreasing "kindling" in subcortical structures. Psychiatric comorbidities in the patient cohort are shown in *Table 4*.

Partial antipsychotic dose reduction or full discontinuation following treatment with oxcarbazepine occurred in 94 out of 154 cases (61%) originally treated with second- or third-generation antipsychotics. In 88 of 154 of these cases (57%), antipsychotics were subsequently completely discontinued, with risperidone being the most commonly discontinued antipsychotic. Selective serotonin reuptake inhibitor antidepressant medication discontinuation occurred in 42 of 164 patients (26%). Divalproex sodium was discontinued in 5 of 5 individuals after initiation of oxcarbazepine. Concurrently prescribed psychostimulants were rarely discontinued, with only 14 of 216 prescriptions (6.5%) discontinued or reduced after oxcarbazepine was introduced. In patients originally treated with second- or third-generation antipsychotics, those who were able to successfully discontinue or reduce their dose of antipsychotic experienced improvements in BMI ratio. In data from the 64 patients who had tapered off of antipsychotics, 46 of 64 (71.9%) had a decrease in BMI and 30 of 64 (46.9%) had a >5% reduction *(Figure 1)*.

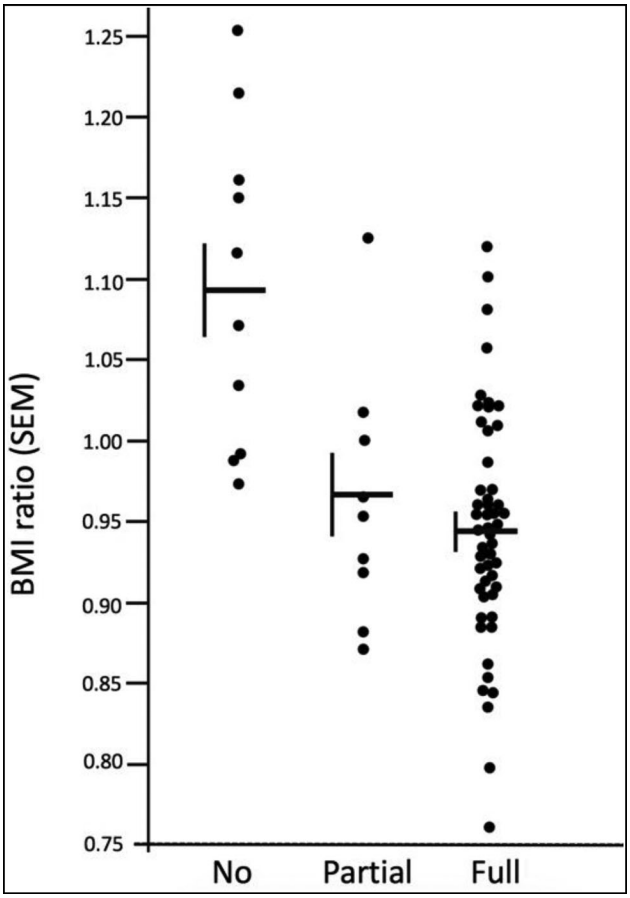

Figure 1. Effect of atypical antipsychotic dose reduction on body mass index (BMI). Doses of second- or third-generation antipsychotics were either not reduced (No, N = 9), partially reduced (Partial, N = 10), or fully reduced (Full, N = 53) after addition of oxcarbazepine. BMI was calculated at the initial date of oxcarbazepine prescription and then at 6 months. The ratio of final/initial BMI is plotted for each group. Both partial and full dose reduction resulted in improved BMI over the 6-month interval ($F(2,71) = 16.78$, $P < 0.0001$). Tukey-Kramer HSD indicates that No > Partial = Full.

DISCUSSION

The findings support the impressions of our institution's child and adolescent psychiatrists that oxcarbazepine can be a safe and effective treatment for child and adolescent psychiatric symptoms across a wide range of psychiatric conditions. It appears that the primary clinical utility of oxcarbazepine as reported by patients and families is the treatment of irritability, anger, and aggressive outbursts and achievement of mood stabilization. These symptoms are common manifestations of ADHD, depressive and anxiety disorders, PTSD, oppositional defiant disorder, and autism in their single or comorbid presentations.

Behavioral symptoms in ADHD, ASD, and other child and psychiatric conditions are commonly treated with second- and third-generation antipsychotics.[26] The wisdom of prescribing these antipsychotics in this population has been questioned, in part because these agents have well-established negative outcomes including metabolic disorders, weight gain, and diabetes mellitus.[27,28] Oxcarbazepine therapy allowed for reduction of dose or full discontinuation of concomitant psychotropic medications, particularly second- and third-generation antipsychotics, and many patients continued on oxcarbazepine therapy for a year or more, with <10% discontinuing oxcarbazepine treatment for lack of response. Less than 10% discontinued oxcarbazepine due to side effects. There was evidence of improvement in BMI ratio in patients able to discontinue second- and third-generation antipsychotics.

More than 57% and 25% of patients starting oxcarbazepine were able to fully discontinue second- or third-generation antipsychotic and antidepressant medications, respectively. Psychostimulants were rarely discontinued after initiation of oxcarbazepine. Although reducing excessive psychotropic medication load is a laudable and widely applied clinical goal, it is worth pointing out that the observed medication changes were measured post hoc and were not driven by any systematic effort at medication reduction. Considering both full and partial dose reductions of second- and third-generation antipsychotics, >60% of patients were able to reduce antipsychotic dose or fully discontinue antipsychotics after starting oxcarbazepine.

A potentially important secondary outcome was a statistically significant improvement in BMI in patients who were able to reduce second- or third-generation antipsychotic dosage. Patients who did not discontinue or decrease doses of antipsychotics had a mean 9% gain in BMI over 6 months, while patients able to reduce doses of these medications experienced a mean 5% reduction in BMI, a 14% differential over 6 months. This effect on BMI may continue to widen over time, as most patients were not restarted on antipsychotics after starting oxcarbazepine. Weight gain is a problematic metabolic side effect of many antipsychotics in the child and adolescent population, and a reduction in BMI due to discontinuation of antipsychotic use after switching to oxcarbazepine may generate significant improvements in metabolic and physical health.[29–33]

This study provides support for clinical experiences in our child and adolescent outpatient clinic, suggesting that oxcarbazepine used as monotherapy or as an adjunct to ongoing additional psychotropics may be a viable option for controlling a variety of psychiatric symptoms in the outpatient child and adolescent population, with irritability/anger, mood stabilization, and aggressive outburst being the most commonly reported improved symptoms. These findings contrast with a previous negative study of oxcarbazepine treatment of mania, providing observational evidence for oxcarbazepine utility in the child psychiatric population.[22] Because of the wide use of second- and third-generation antipsychotics to treat symptoms of irritability, aggression, and mood with the potential for metabolic side effects, the present study showed that oxcarbazepine may be a more benign yet effective option to replace these agents.

Oxcarbazepine was well tolerated by most patients and was effective for treatment of a wide variety of psychiatric symptoms. Instances of discontinuation due to troubling side effects were observed in <10% of patients. This may be due to the use of relatively low doses of oxcarbazepine (600 mg/day) compared to doses reported to address behavioral problems in ASD patients (mean 1350 mg/day).[23] More than half of the patients in our study were being treated for ADHD, and psychiatric symptoms were successfully treated with oxcarbazepine in these patients. This is an important observation, because while oxcarbazepine has been reported to be effective in treating adult ADHD patients,[7] studies of oxcarbazepine in child and adolescent ADHD populations are not common.

Strengths of our study include electronic health record data capture of a large child psychiatric population, use of oxcarbazepine across a wide range of psychiatric diagnoses, data on BMI outcomes, data on concurrent psychotropic medications, and a clinically meaningful study interval. Weaknesses of the study include the naturalistic, retrospective, nonblinded design and a lack of formal rating scales to precisely quantitate changes in psychiatric symptoms. Nonetheless, our findings could contribute to the discussion of oxcarbazepine use in child psychiatry, particularly as an alternative to second- or third-generation antipsychotics.

In summary, oxcarbazepine may be a pragmatic option for treatment of a wide range of psychiatric symptoms in children and adolescents, particularly in patients taking second- or third-generation antipsychotics, allowing for a subsequent reduction of antipsychotic dosage leading to improvements in BMI. The findings highlight the need for controlled clinical trials of oxcarbazepine in a more rigorous study design to assess its effects in the child and adolescent population. This may be particularly true for child ADHD, since the present study is one of the first to examine oxcarbazepine treatment of psychiatric symptoms in children with this disorder.

1. McAuley JW, Biederman TS, Smith JC, et al. Newer therapies in the drug treatment of epilepsy. *Ann Pharmacother*. 2002;36(1):119–128. doi:10.1345/aph.10417.
2. Campos MS, Ayres LR, Morelo MR, et al. Efficacy and tolerability of antiepileptic drugs in patients with focal epilepsy: systematic review and network meta-analyses. *Pharmacother*. 2016;36(12):1255–1271. doi:10.1002/phar.1855.
3. Nevitt SJ, Sudell M, Weston J, et al. Antiepileptic drug monotherapy for epilepsy: a network meta-analysis of individual participant data. *Cochrane Database Syst Rev*. 2017;12:CD011412. doi:10.1002/14651858.CD011412.pub3.
4. Moavero R, Pisani LR, Pisani F, et al. Safety and tolerability profile of new antiepileptic drug treatment in children with epilepsy. *Expert Opin Drug Saf*. 2018;17(10):1015–1028. doi:10.1080/14740338.2018.1518427.
5. Xu J, Shi X, Qiu Y, et al. Association between HLA-A*3201 allele and oxcarbazepine-induced cutaneous adverse reactions in Eastern Han Chinese population. *Seizure*. 2019;65:25–30. doi:10.1016/j.seizure.2018.12.011.
6. Kanner AM, Ashman E, Gloss D, et al. Practice guideline update summary: efficacy and tolerability of the new antiepileptic drugs I: Treatment of new-onset epilepsy: report of the American Epilepsy Society and the Guideline Development, Dissemination, and Implementation Subcommittee of the American Academy of Neurology. *Epilepsy Curr*. 2018;18(4):260–268. doi:10.5698/1535-7597.18.4.260.
7. Davids E, Kis B, Specka M, et al. A pilot clinical trial of oxcarbazepine in adults with attention-deficit disorder. *Prog Neuropsychopharmacol Biol Psychiatry*. 2006;30:1003–1038.
8. Kaufman KR, Gerner R. Adjunctive oxcarbazepine in comorbid anxiety and affective disorder with hyponatremic seizure: case analysis and literature review. *Epilepsy Behav*. 2003;4(6):766–770. doi:10.1016/j.yebeh.2003.08.007.
9. Berigan T. Oxcarbazepine treatment of posttraumatic stress disorder. *Can J Psychiatry*. 2002;47(10):973–974. doi:10.1177/070674370204701014.
10. Malek-Ahmadi P, Hanretta AT. Possible reduction in posttraumatic stress disorder symptoms with oxcarbazepine in a patient with bipolar disorder. *Ann Pharmacother*. 2004;38(11):1852–1854. doi:10.1345/aph.1D442.
11. Gitlin M, Frye MA. Maintenance therapies in bipolar disorders. *Bipolar Disord*. 2012;14:51–65. doi:10.1111/j.1399-5618.2012.00992.x.
12. Belli H, Ural C, Akbudak M. Borderline personality disorder: bipolarity, mood stabilizers and atypical antipsychotics in treatment. *J Clin Med Res*. 2012;4(5):301–308. doi:10.4021/jocmr1042w.
13. Eatmon CV, Daniel JS. Should you use an anticonvulsant to treat impulsivity and aggression? *Curr Psychiatry*. 2014; 13:49–51.
14. Liu X, Carney PR, Bussing R, Segal R, Cottler LB, Winterstein AG. Trends in antiepileptic drug use in children and adolescents with epilepsy. *Pediatr Neurol*. 2017;74:32–40. doi:10.1016/j.pediatrneurol.2017.05.016.
15. Besag F, Aldenkamp A, Caplan R, Dunn DW, Gobbi G, Sillanpää M. Psychiatric and behavioural disorders in children with epilepsy (ILAE Task Force Report): adverse cognitive and behavioural effects of antiepileptic drugs in children. *Epileptic Disord*. 2016;18(S1):1–86. doi:10.1684/epd.2016.0817.
16. Wei SH, Liu CC, Fan PC. A comparison of the efficacy and tolerability of oxcarbazepine oral suspension between infants and children with epilepsy: a retrospective chart review at a single medical center in Taiwan. *Pediatr Drugs*. 2014;16(1):83–89. doi:10.1007/s40272-013-0049-x.
17. Verrotti A, Moavero R, Panzarino G, Di Paolantonio C, Rizzo R, Curatolo P. The challenge of pharmacotherapy in children and adolescents with epilepsy-ADHD comorbidity. *Clin Drug Invest*. 2018;38(1):1–8. doi:10.1007/s40261-017-0585-1.
18. Birmaher B, Brent D, Bernet W, et al. Practice parameter for the assessment and treatment of children and adolescents with depressive disorders. *J Am Acad Child Adolesc Psychiatry*. 2007;46(11):1503–1526. doi:10.1097/chi.0b013e318145ae1c.
19. Steiner H, Remsing L. Practice parameter for the assessment and treatment of children and adolescents with oppositional defiant disorder. *J Am Acad Child Adolesc Psychiatry*. 2007;46(1):126–141. doi:10.1097/01.chi.0000246060.62706.af.
20. Volkmar F, Siegel M, Woodbury-Smith M, King B, McCracken J, State M. Practice parameter for the assessment and treatment of children and adolescents with autism spectrum disorder. *J Am Acad Child Adolesc Psychiatry*. 2014;53(2):237–257. doi:10.1016/j.jaac.2013.10.013.
21. Kowatch RA, Fristad M, Birmaher B, Wagner KD, Findling RL, Hellander M. Treatment guidelines for children and adolescents with bipolar disorder. *J Am Acad Child Adolesc Psychiatry*. 2005;44(3):213–235. doi:10.1097/00004583-200503000-00006.
22. Wagner KD, Kowatch RA, Emslie GJ, et al. A double-blind, randomized, placebo-controlled trial of oxcarbazepine in the treatment of bipolar disorder in children and adolescents. *Am J Psychiatry*. 2006;163(7):1179–1186. doi:10.1176/ajp.2006.163.7.1179.
23. Douglas JF, Sanders KB, Benneyworth MH, et al. Brief report: retrospective case series of oxcarbazepine for irritability/agitation symptoms in autism spectrum disorder. *J Autism Dev Disord*. 2013;43(5):1243–1247. doi:10.1007/s10803-012-1661-2.
24. Kapetanovic S. Oxcarbazepine in youths with autistic disorder and significant disruptive behaviors. *Am J Psychiatry*. 2007;164(5):832–833. doi:10.1176/ajp.2007.164.5.832.

25. Coleman DM, Adams JB, Anderson AL, et al. Rating of the effectiveness of 26 psychiatric and seizure medications for autism spectrum disorder: results of a national survey. *J Child Adolesc Psychopharmacol*. 2019;29(2):107–123. doi:10.1089/cap.2018.0121.
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. Caccia S. Safety and pharmacokinetics of atypical antipsychotics in children and adolescents. *Paediatr Drugs*. 2013;15(3):217–233. doi:10.1007/s40272-013-0024-6.
29. 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.
30. 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.
31. 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.
32. 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.
33. Loy JH, Merry SN, Hetrick SE, et al. Atypical antipsychotics for disruptive behaviour disorders in children and youths. *Cochrane Database Syst Rev*. 2017;8:CD008559. doi:10.1002/14651858.CD008559.pub2.