Adult Outcomes of Disruptive Mood Dysregulation Disorder

Children who meet criteria for the new disruptive mood dysregulation disorder (DMDD) diagnosis are at increased risk for many adverse outcomes in young adulthood, according to results of a longitudinal study. As adults, these individuals have higher rates of anxiety and depression, health problems, police contacts, impoverishment, and low educational attainment compared with both normal controls and children with other psychiatric illnesses.

Methods: Data were analyzed from the Great Smoky Mountains Study, a longitudinal study of >1400 children living in North Carolina. Initial interviews were conducted for 3 different age cohorts: 9, 11, and 13 years. Participants were then evaluated at regular intervals until age 25 years. DMDD was diagnosed by retrospectively applying DSM-5 diagnostic criteria to data from the Child and Adolescent Psychiatric Assessment (CAPA) interview, conducted between the ages of 10 and 16 years. Adult outcomes were assessed primarily by self-report.

Results: A small percentage of patients (4%) met DSM-5 criteria for DMDD at some point between the ages of 10 and 16 years. A total of 75 patients with DMDD, 372 patients with other psychiatric disorders, and 826 comparison subjects without psychiatric disorders were followed into adulthood. Individuals with DMDD did not differ from other groups in gender or ethnicity, but like those with other psychiatric diagnoses, they were more likely than healthy comparison subjects to come from impoverished families and single-parent households.

As young adults, individuals with DMDD were more likely to have an anxiety or depressive disorder and to have ≥2 psychiatric disorders than the psychiatric or normal control groups. They were not at elevated risk for substance use disorders. DMDD subjects had elevated rates of 4 of 9 measured poor health outcomes: sexually transmitted diseases, cigarette smoking, illness contagion, and non-substance psychiatric disorders. The DMDD group also had elevated rates of felony charges and self-reported police contact, physical fighting, and illegally breaking into buildings. They had higher rates of adverse outcomes on 5 of the
study's 7 indicators of financial status and educational attainment, including higher rates of impoverishment, high-school dropout, and trouble keeping a job; and more disrupted adult social functioning. Comparing summary scores in the 4 domains of health, risky behavior, financial, and social outcomes, DMDD subjects had statistically significantly worse outcomes than comparison subjects and numerically (although not usually statistically) worse outcomes than cases with other disorders.

Editorial: While the DSM-5 category of DMDD has been criticized because it pathologizes normal temper tantrums, may encourage overuse of medication, and has little empirical support, it is gaining support via epidemiologic studies like the present one.\(^2\) For clinicians, DMDD provides a category for children with non-episodic temper outbursts or aggression who should not receive a diagnosis of bipolar disorder. Although diagnostic boundaries of DMDD have not yet been clearly delineated, it is clear that the diagnosis identifies children at high risk of lifetime psychopathology. Unfortunately, there is little evidence-based research on treatment, and not much likelihood of large-scale NIMH-funded treatment research until underlying mechanisms are discovered.

\(^1\)Copeland W, Shanahan L, Egger H, Angold A, et al: Adult diagnostic and functional outcomes of DSM-5 disruptive mood dysregulation disorder. *American Journal of Psychiatry* 2014;171 (June):668–674. From Duke University Medical Center, Durham, NC; and other institutions. Funded by the NIMH; and other sources. The authors disclosed no financial relationships with commercial sources.


### Justice and Rejection Sensitivity in ADHD

Children and adolescents with ADHD appear to be prone to increased justice and rejection sensitivity. These cognitive distortions may contribute to the emergence of behavioral problems typically associated with the disorder by making children more sensitive to negative social cues and more likely to react badly to them, according to a cross-sectional study.

**Background:** Justice sensitivity is a cognitive preoccupation with injustice, leading to rumination on perceived injustices, particularly with oneself as victim. Justice sensitivity can be measured from the perspective of oneself or others as the victim, leading to anger and an urge to retaliate; or from the perspective of the perpetrator, leading to guilt and a need to compensate the victim. High justice sensitivity has been observed in adults with ADHD. The related and more familiar concept of rejection sensitivity—the tendency to expect, readily perceive, and overreact to rejection—has also been linked with ADHD in adults. The present study attempted to replicate these findings in children and adolescents.

**Methods:** The study was conducted as part of a larger investigation of risk factors for psychological problems in 1235 German children and adolescents, aged 10–19 years. All symptoms were assessed using self-report questionnaires. ADHD and conduct problems were measured with the Strengths and Difficulties Questionnaire (SDQ). Participants also completed the Justice Sensitivity Inventory for Children and Adolescents, the Child Rejection Sensitivity Questionnaire (with responses divided into anxious and angry categories), a German depression inventory for children, and a self-esteem questionnaire.

**Results:** A total of 87 study participants (7%) reported severe ADHD symptoms. These participants had greater victim justice sensitivity, both anxious and angry types of rejection sensitivity, and less perpetrator justice sensitivity than controls. Children with ADHD were more likely to perceive injustices from all 3 perspectives, contrary to the adult data, which showed less perception of injustice from the observer's and perpetrator's perspective. Separate latent path analyses showed that justice and rejection sensitivity, independently of each other, mediated the relation-
ship between ADHD and conduct problems and depression. A third analysis found the association between ADHD and low self-esteem was mediated only by rejection sensitivity.

Discussion: These findings suggest children and adolescents with ADHD are particularly sensitive to experiences of injustice and rejection as a victim. They also have lower thresholds for perceiving situations as unjust. Victim sensitivity and rejection sensitivity may promote dysfunctional thoughts and beliefs that may burden social relationships and lead to maladaptive behavior. These patients may benefit from cognitive interventions and cognitive restructuring exercises that help overcome their hostile attribution bias and train them to think of alternative explanations for people’s negative behavior, as well as avoiding behavior that contributes to others’ unfavorable reactions.

Bondu R, Esser G: Justice and rejection sensitivity in children and adolescents with ADHD symptoms. *European Child and Adolescent Psychiatry* 2014; doi 10.1007/s00787-014-0560-9. From the University of Potsdam, Germany. Funded by the German Research Foundation. The authors declared no conflicts of interest.

## Edivoxetine in ADHD

The investigational selective norepinephrine reuptake inhibitor edivoxetine was effective in a group of young patients with ADHD.¹

**Methods:** An 8-week randomized clinical trial was carried out in 340 pediatric patients (aged 6–16 years) who met DSM-IV-TR diagnostic criteria for ADHD. Patients with no history of stimulant use were randomly assigned to 1 of 5 treatment groups: edivoxetine 0.1, 0.2, or 0.3 mg/kg/day; OROS methylphenidate as an active control to validate the study; or placebo. Because the efficacy of ADHD drugs may be more robust in stimulant-naive patients, those with previous stimulant exposure were separately randomized to 1 of 4 treatment groups, excluding OROS methylphenidate. All patients assigned to receive edivoxetine were started at 0.1 mg/kg/day, and the 2 higher doses were titrated in a stepwise manner. Target daily doses of OROS methylphenidate were 35 or 54 mg, depending on weight. Patients unable to tolerate the assigned doses were discontinued from the study. The primary efficacy measure was the parent version of the ADHD Rating Scale-IV (ADHD-RS-IV). Response was defined as a ≥60% reduction from baseline in the ADHD-RS-IV or a Clinical Global Impression–Improvement* score of ≤2 at study endpoint.

**Results:** About three-fourths of patients in the 5 treatment groups completed the study. Patients had an average age of 12 years, and nearly half of them had previously received stimulants. Improvement with OROS methylphenidate was greater than placebo, indicating that this was a valid trial.

The 2 higher edivoxetine doses, but not the 0.1-mg dose, were superior to placebo at study endpoint. In the stimulant-naive patients, effect sizes* for the ADHD-RS-IV were 0.47, 0.41, and 0.69 for 0.2 mg/kg edivoxetine, 0.3 mg/kg edivoxetine, and OROS methylphenidate, respectively. In previously treated patients, the effect sizes for the 2 edivoxetine doses were 0.51 and 0.54, respectively. Efficacy did not differ between children and adolescents. Response rates differed significantly from placebo in the 0.2-mg edivoxetine group (57% vs. 35%; p=0.007). Response rates did not differ from placebo with the other active treatments, or with either edivoxetine dose in patients with no previous stimulant exposure. The median time to response was significantly shorter with the 2 higher edivoxetine doses than placebo: about 30 vs. 60 days (p=0.012).

Edivoxetine shares the same mechanism of action as atomoxetine, and the safety profiles appear to be similar. Commonly reported adverse effects of edivoxetine included somnolence; upper abdominal pain; nausea; vomiting; irritability; and decreased appetite. These were generally mild to moderate.
**Editor’s Note:** Edivoxetine was at one time investigated as a potential add-on treatment to SSRIs in patients with major depression. However, after the results of 3 late-stage trials indicated the drug was not more effective than placebo at reducing standardized depression scores, Eli Lilly and Company opted not to proceed with development of edivoxetine as adjunctive treatment for depression.2


2Lilly announces edivoxetine did not meet primary endpoint of phase III clinical studies as add-on therapy for major depressive disorder [press release]. Indianapolis, IN: Eli Lilly and Company; December 5, 2013.

**Drug Trade Names:** atomoxetine—Strattera; OROS methylphenidate—Concerta

*See Reference Guide.

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### Targeted Treatment for Inattentive-Type ADHD

Child Life and Attention Skills (CLAS), a novel integrated psychosocial treatment developed specifically for the inattentive subtype of ADHD, was superior to parent-focused treatment or treatment as usual in a randomized trial.

**Background:** CLAS is based on techniques drawn from rehabilitation psychology, such as scaffolding, reminders, and routinization, to help manage children’s executive function problems. Compared with other ADHD therapies, there is less emphasis on managing impulsive and defiant behavior and more reliance on directly teaching skills to the child, rather than using parents and teachers as intermediaries.

**Methods:** The study enrolled successive cohorts of 5–8 families (199 children; mean age, 9 years) who were randomly assigned to CLAS; parent-focused treatment (PFT), consisting of only the parent components of CLAS; or treatment as usual in the community. In the CLAS intervention, parents and children participated separately in 10 parent- and child-only group meetings (90 minutes each), as well as up to 6 meetings with both the parent and child (30 minutes each). During the sessions, children were taught self-management, social, and attentional skills, which were reinforced with homework in multiple settings. Teachers also received an orientation, followed by up to 5 subsequent meetings with the parent, child, and therapist. Monthly booster sessions were also offered.

Outcomes were evaluated at the end of treatment (after 10–13 weeks) and 5–7 months later. The assessments included parent- and teacher-rated versions of most instruments: the Inattention items from the Child Symptom Inventory (CSI), Children’s Organizational Skills Scale, Social Skills Improvement System scales, Impairment Rating Scale, and Clinical Global Impression scale.

**Results:** CLAS was superior to treatment as usual for outcomes measured immediately post-treatment, with effect sizes* (ES) ranging from 0.34 to 1.07. CLAS was also superior to PFT for 5 of the 8 study outcomes: teacher-rated inattentive symptoms (ES, 0.42); both parent- and teacher-rated organizational skills (ES, 0.4 and 0.44, respectively); teacher-rated social skills (ES, 0.31); and teacher-rated overall improvement (ES, 0.57). In the analysis of long-term follow-up assessments, CLAS remained superior to other treatments for most outcomes in parent ratings only, with medium to near-medium effect sizes.

Clinically meaningful response was defined as CSI inattention symptoms within 1 standard deviation of norms for age and gender. At post-treatment, parents rated 55% of children who received CLAS as responders, compared with 43% with PFT and 30% with treatment as usual (p=0.03). Teacher ratings showed a similar pattern of response. Differences in the proportion of
meaningful responders between CLAS and treatment as usual, but not CLAS and PFT, were statistically significant. Both parents and teachers rated CLAS as highly satisfactory.

Study Rating*—17 (100%): This study met all criteria for a randomized controlled trial.

Piffner L, Hinshaw S, Owens E, Zalecki C, et al: A two-site randomized clinical trial of integrated psychosocial treatment for ADHD-inattentive type. *Journal of Consulting and Clinical Psychology* 2014; doi 10.1037/a0036887. From the University of California, San Francisco; and the University of California, Berkeley. *Funded by the NIMH. The authors did not include disclosure of potential conflicts of interest.*

*See Reference Guide.

**Hallucinations in Children and Adolescents**

According to a literature review, hallucinations are common in children and adolescents and usually resolve spontaneously. However, underlying stressors increase the likelihood that hallucinations will persist and require clinical intervention.

Imaginary companions are very common hallucination-like phenomena that are associated with positive developmental outcomes; these should not be considered markers of psychosis. Sleep-related hallucinations are also common, decline with increasing age, and are not usually of concern unless they are part of a childhood sleep disorder such as narcolepsy. Hallucinations can also occur in neurologic disorders such as migraine, complex partial seizures, infections, and autoimmune or metabolic disorders.

The prevalence of hallucinations also appears to be elevated in children with nonpsychotic disorders such as ADHD, major depressive disorder, disruptive behavioral disorders, and Tourette syndrome. In these patients, hallucinations are particularly strong markers for the presence of other psychopathology. In the presence of a psychiatric disorder, hallucinations are associated with risk of suicidal behavior. Not surprisingly, the prevalence of visual and auditory hallucinations is very high in the NIMH childhood-onset schizophrenia cohort, perhaps reflecting the severe psychopathology of this group of children.

Hallucinations that first occur or are persistent in adolescence are increasingly associated with psychopathology. Cultural context, a history of migration, early trauma, and genetic factors all play into the development of problematic hallucinations. Cognitive findings related to hallucinations include lower performance on tests of executive function, language, fine motor skills, and information processing speed, also risk factors for psychosis. Theory of mind—the ability to correctly interpret another individual’s intentions or emotions—may protect against the development of delusions.

The Persistence-Impairment model has been developed to describe the probabilistic, dose-related relationship between the persistence of hallucinations and risk factors that increase stress, such as trauma, ethnic minority status, and substance misuse. Studies that support this model show that the presence of isolated hallucinations in childhood is insufficient to predict clinical outcomes and needs to be considered in the context of the child’s environment; psychology; sleep/wake cycles; developmental and sociocultural status; and other factors.

In the absence of pathological signs, the best treatment is destigmatization, normalization, and reassurance. Hallucinations are of greater concern in a child with suicidality, substance use, pathological symptoms, or comorbid disorders. Hallucinations may require specific interventions that diverge from treatments oriented toward the underlying disorders. Effective treatments may include cognitive-behavioral therapy, hallucination-focused integrative therapy, and theory-of-mind-centered treatments.

Jardri R, Bartels-Velthuis A, Debbane M, Jenner J, et al: From phenomenology to neurophysiological understanding of hallucinations in children and adolescents. *Schizophrenia Bulletin* 2014;40 (suppl 4):S221–S232. From the University Medical Center Lille, France; and other institutions. *Funded by the Wellcome Trust. The authors declared no conflicts of interest.*
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Clinical Global Impression–Improvement (CGI-I) Scale: A 7-point rating of patient improvement. A score of 1 corresponds to a rating of very much improved; 2=much improved; 3=minimally improved; 4=no change; 5=minimally worse; 6=much worse; 7=very much worse.

Effect Size: The effect size represents the amount of change in outcome that can be attributed to treatment, where 0.2 indicates a small effect, 0.5 a medium effect, and 0.8 a large effect. It is relatively independent of clinical significance, and large effect sizes do not ensure treatment efficacy.

Study Rating: A measure of how well a study conforms to quality standards. The study rating uses a checklist system based on the comprehensive Strength of Evidence Report from the Evidence-based Practice Center Program of the Agency for Healthcare Research and Quality (AHRQ). The rating checklists have been posted at www.alertpubs.com.

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