

CHILD & ADOLESCENT PSYCHIATRY ALERTS

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Ketamine for Resistant Depression

In a preliminary study, intravenous ketamine infusion resulted in clinical response in adolescents with resistant depression. Treatment was generally safe and well tolerated.

Methods: Study participants, aged 12–18 years, had depression that had been resistant to ≥ 2 previous antidepressants and a current score of >40 on the Children's Depression Rating Scale-Revised (CDRS-R). All patients received 6 open-label ketamine infusions over 2 weeks. Dosing for the first 5 patients was based on a formula for ideal body weight (mean dosage, 0.35 mg/kg), but when those patients failed to achieve response, the dosing strategy for the remaining patients was changed to actual body weight and the mean increased to 0.5 mg/kg. The primary outcome measure was the CDRS-R, and patients who met response criteria of a $\geq 50\%$ decrease in score were invited to participate in 6 weekly follow-up visits and a 6-month final visit. During follow-up, patients received usual care from their own providers. Remission was defined as a CDRS score ≤ 28 , and relapse as a CDRS score $\geq 50\%$ of the pretreatment baseline.

Results: The 13 patients had a mean age of 17 years; 5 were girls. Of note, the mean body mass index was 30.7. Patients had received an average of 5.7 previous antidepressants, 6 patients had a history of trauma, and 6 had a history of suicide attempts.

In the group as a whole, the mean CDRS-R score decreased from 63.9 to 44.1 following the final infusion ($p=0.0004$). Of the 8 patients who received actual body-weight dosing, 5 met response criteria and completed 6 weeks of follow-up, 4 of whom also completed the 6-month follow-up. At the post-treatment evaluation, 3 of the 5 achieved remission; 2 of these patients remained in remission at 6 weeks. A third responder reached remission at 6 weeks. The other 2 initial responders experienced relapse at 1 and 2 weeks. At the 6-month evaluation, 2 adolescents remained in remission.

Patients also showed significant improvements at week 6 on secondary outcome measures including the Montgomery-Asberg Depression Rating scale, the Beck Depression Inventory, and the Clinical Global Impression–Severity scale, but not in symptoms of anhedonia. Significant predictors of response were body mass index and the actual ketamine dose. A history of trauma was a trend-level predictor of treatment response.

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Transient blood pressure changes were observed during infusion, but there were no significant changes in heart rate or respiration. Two patients reported feeling dysphoria during infusions, and 3 experienced nausea. One patient who had high levels of suicidal thinking at study entry reported a worsening of suicidal thoughts, although the change was not evident in clinical assessments.

Discussion: Intravenous ketamine has been shown to be effective in resistant depression in adults, in whom dosing based on ideal body weight may be sufficient. The present results suggest actual-body-weight dosing may be more effective in adolescents. Parental concerns about the potential for ketamine to induce substance use disorders were not addressed in the study, nor was the possibility for ketamine to worsen existing substance use disorders in patients with an increased vulnerability. While these preliminary results are positive, they require replication in large, double-blind, controlled trials that address the longer-term effects and safety issues.

Cullen K, Amatya P, Roback M, Albott C, et al: Intravenous ketamine for adolescents with treatment-resistant depression: an open-label study. *Journal of Child and Adolescent Psychopharmacology* 2018;28 (September):437–444. From the University of Minnesota Medical School, Minneapolis; and other institutions. **Funded by the University of Minnesota. The authors declared no competing interests.**

Asenapine Response in Bipolar Disorder

In patients with bipolar I disorder, the efficacy of asenapine (*Saphris*) was not influenced by the type of current episode or the number of previous episodes, according to a post-hoc clinical-trial analysis.¹ Body weight also did not affect outcome, which suggests there may be no need for weight-based dosing in children and adolescents.

Background: Evidence in adults with bipolar I disorder suggests that treatment outcomes may be related to illness-associated factors such as the number of previous mixed or manic episodes and the characteristics of the current episode (mixed vs pure mania). However, factors that influence treatment response in younger patients have not been well studied. The present post-hoc analysis was undertaken to evaluate predictors of treatment outcome with asenapine in pediatric bipolar disorder.

Methods: The clinical trial compared 3 dosages of asenapine (2.5, 5, and 10 mg b.i.d.) and placebo in patients, aged 10–17 years, with DSM-IV-TR bipolar I disorder.² The study's primary efficacy outcome was change from baseline to day 21 in the Young Mania Rating Scale (YMRS); change in the Clinical Global Impression scale for use in bipolar illness (CGI-BP) was the key secondary outcome. Post-hoc analyses were conducted to evaluate the relationship of efficacy to the type of current episode (mixed or manic), the number of previous episodes (<3, 3–5, and >5), and baseline body weight and body mass index, stratified by tertile.

Results: The 403 study patients had a mean age of 14 years and a mean age at onset of 11 years. The majority of patients (56%) were experiencing a mixed episode, and nearly one-third had experienced ≥ 3 previous manic or mixed episodes. The clinical trial met its primary efficacy endpoint, with statistically significant improvement in the YMRS and the CGI-BP for all 3 asenapine doses, relative to placebo. In the post-hoc analysis, efficacy did not differ as a function of episode type. Patients with either a mixed or manic episode experienced similar decreases in YMRS score (approximate least squares mean changes, * 12–15 points in all groups except those with pure mania receiving 2.5 mg asenapine whose improvement was similar to placebo). The number of previous episodes also did not have a substantial effect on the between-group differences in YMRS change. Least squares mean changes averaged about 6–10 points with placebo, compared with about 10–20 points with asenapine. Asenapine efficacy also did not differ in a consistent manner according to the tertile of body weight. Improvements in

YMRS were generally similar in all groups, except those in the lowest tertile who received the highest asenapine dose, in whom improvements were smaller.

Discussion: The post-hoc analysis of these clinical-trial data indicated that asenapine efficacy did not differ according to gender, age of onset of bipolar disorder, presence or absence of ADHD, or use of stimulants. The results also suggest illness-related factors do not affect efficacy.

¹Findling R, Earley W, Suppes T, Patel M, et al: Post hoc analyses of asenapine treatment in pediatric patients with bipolar I disorder: efficacy related to mixed or manic episode, stage of illness, and body weight. *Neuropsychiatric Disease and Treatment* 2018;14:1941–1962. From Johns Hopkins University and the Kennedy Krieger Institute, Baltimore, MD; Allergan, Madison, NJ; and other institutions. **Funded by Merck & Co., Inc.; and Allergan. All study authors disclosed potentially relevant financial relationships.**

²Findling R, et al: Asenapine for the acute treatment of pediatric manic or mixed episode of bipolar I disorder. *Journal of the American Academy of Child and Adolescent Psychiatry* 2015;54:1032–1041. See *Child & Adolescent Psychiatry Alerts* 2016;18 (February):8–9.

*See Reference Guide.

NMDA Agonist-Enhanced CBT for Panic Disorder

In a placebo-controlled pilot study, D-cycloserine (DCS) did not enhance the effects of intensive cognitive behavioral therapy in adolescents with panic disorder.

Background: This study was an attempt to improve on the efficacy of intensive CBT, which has a long-term response rate of about 72% in adolescents with panic disorder. Augmentation of CBT with DCS has been helpful in adults, but studies in children and adolescents with other anxiety disorders have had inconsistent results.

Methods: The study enrolled 24 adolescents, aged 12–17 years, with a primary diagnosis of DSM-IV panic disorder. Concurrent medication was permitted. All patients underwent intensive CBT, consisting of 6 sessions (2–6 hours each) and 2 days of independent practice, over an 8-day period. Therapy included psychoeducation, cognitive restructuring, interoceptive exposures, in-vivo exposures with the therapist and independently, and relapse prevention. A 30-minute parent component was included at the end of each session. Patients were randomly assigned to receive double-blind 50 mg DCS or placebo, to be taken 1 hour before the start of the 3 exposure-based therapy sessions on days 3–5.

Results: Patients in both groups experienced substantial improvement in all study outcomes, with effect sizes* ranging from 1.64 to 3.58. The addition of DCS did not increase rates of recovery (67% vs 90% for placebo) or response (75% vs 90%). Patients in both groups showed improvement in the number of comorbid diagnoses and in additional measures of panic and anxiety symptoms. DCS did not increase the speed of improvement or increase patient satisfaction with treatment. No adverse effects were reported. At the 3-month follow-up, there continued to be no difference between the DCS and placebo groups on any outcome measure, although 2 patients who received DCS continued to improve after the end of treatment.

Discussion: DCS may enhance not only fear extinction, but also fear-related memories. It is possible that it could be more effective if given only after successful exposures. In addition, the high overall response rate to the intensive CBT may have contributed to the lack of DCS effects.

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

Leyfer O, Carpenter A, Pincus D: N-methyl-D-aspartate partial agonist enhanced cognitive-behavioral therapy of panic disorder in adolescents. *Child Psychiatry & Human Development* 2018; doi 10.1007/s10578-018-0837-1. From Boston University and Massachusetts General Hospital, MA. **Funded by the Brain and Behavior Research Foundation. The authors did not include disclosure of potential conflicts of interest.**

*See Reference Guide.

tDCS for Anorexia Nervosa

In a pilot study, adding transcranial direct current stimulation to treatment as usual improved weight gain in adolescents with anorexia nervosa.

Methods: Study participants were 23 adolescents (1 boy), aged 10–17 years, with a DSM-5 diagnosis of anorexia nervosa and a body mass index (BMI) of 12–18. The experimental group received tDCS that was excitatory over the left dorsolateral prefrontal cortex (DLPFC; anode) and inhibitory over the right DLPFC (cathode). tDCS was delivered in 20-minute sessions, 3 times/week, for 6 weeks. The comparison group received family psychotherapy, with separate weekly group therapy for adolescents and parents and biweekly family meetings. All participants received an atypical antipsychotic; SSRIs and benzodiazepines were prescribed for some. Both groups received ongoing group and individual psychological support and parent psychoeducation (treatment as usual). Treatment outcomes were assessed using standardized measures of eating disorder pathology as well as anxiety and depression.

Results: Mean BMI increased from 14.7 to 16.6 in adolescents receiving tDCS and from 15.5 to 16.1 in the control group (13% vs 4%; $p < 0.01$). These gains in the tDCS group persisted after 1 month of follow-up. Both groups showed significant improvement in the psychopathological rating scales, with no treatment-related difference overall or in any subscale, including drive for thinness, body dissatisfaction, eating disorder risk, low self-esteem, personal alienation, interpersonal insecurity, interpersonal alienation, asceticism, ineffectiveness, interpersonal problems, and global psychological maladjustment. Within the tDCS group, increases in BMI were correlated with improvement in measures of global psychological maladjustment and interpersonal problems, which may suggest tDCS improves cognitive symptoms linked to maladaptive food behavior. tDCS was well tolerated, with few physical complaints and no emergent psychological symptoms. Both treatment groups experienced positive effects on mood and anorexia symptoms, probably due to the nutritional, psychoeducational, and psychopharmacologic interventions common to both.

Discussion: In previous studies, tDCS applied in the opposite direction to the present study was shown to reduce food cravings in overweight individuals and alcohol cravings in patients with alcohol abuse. The authors hypothesize that in these patients, tDCS treatment corrected the right hemisphere hyperactivity believed to underlie the eating disorder, restoring the balance between right- and left-hemisphere activity.

Costanzo F, Menghini D, Maritato A, Castiglioni M, et al: New treatment perspectives in adolescents with anorexia nervosa: the efficacy of non-invasive brain-directed treatment. *Frontiers in Behavioral Neuroscience* 2018; doi 10.3389/fnbeh.2018.00133. From Bambino Gesù Children's Hospital, Rome, Italy. **Source of funding not stated. The authors declared no competing interests.**

Screening Tools Predict Depression Outcomes

Information on anxiety and substance use collected using screening questionnaires appears to help identify adolescents with depression who are at risk for poor outcomes of collaborative care. Screening tools should not replace a thorough clinical interview, but they can supplement the interviews in identifying young people who may need additional resources to achieve sustained remission.

Methods: Four screening instruments—the CRAFFT substance-use screen, the Mood Disorder Questionnaire—modified for adolescents (MDQ-A), the Patient Health Questionnaire-9 (PHQ-9), and the child-report version of the Spence Children's Anxiety Scale (SCAS-C)—were evaluated as potential predictors of outcomes of a collaborative care program for adolescent depression. The program, called EMERALD, was initiated at a pediatric and adolescent medicine primary

care facility affiliated with the Mayo Clinic. Eligible participants were aged 12–17 years (or 18 if still in high school) and had a new or previous diagnosis of a depressive disorder. Severe comorbid disorders were grounds for exclusion, but adolescents were allowed to participate if they had anxiety disorders, ADHD, substance use disorders not requiring primary treatment, or disruptive behavior disorders. The collaborative care program included depression care management by a registered nurse; supervision by a child and adolescent psychiatrist who recommended medications and psychotherapy; medication management by the primary care physician; and psychotherapy provided by a clinical social worker. Remission was defined as a PHQ-9 score of <5, indicating minimal symptoms. Patients graduated from the program when they achieved this score for 3 consecutive months. Adolescents enrolled in EMERALD for >12 months were assumed to be nonresponders and were offered other forms of care.

Results: The study included a total of 182 patients, of whom 101 achieved remission and 49 graduated from the program. Reasons for failure to graduate were loss to follow-up in 85 patients, treatment failure after 12 months in 25, and the patient's decision in 23.

None of the screening tools were significantly associated with remission. Graduation, however, was associated with lower scores on the CRAFFT and on the SCAS-C. Although both graduates and non-graduates had average CRAFFT scores that were below the clinical threshold, each 1-point increase in this measure was associated with a 62% higher likelihood of failure to graduate (odds ratio,* 1.62; $p=0.01$). When the SCAS-C was analyzed as a categorical variable, with a score of ≥ 33 considered positive in boys and ≥ 39 in girls, scores above the cutoff were associated with a >2-fold higher risk of non-graduation (odds ratio, 2.35; $p=0.02$).

Discussion: Collaborative care models are being used increasingly to treat complex conditions. The few studies of collaborative care models in child and adolescent depression have had mixed results. Results of the present study suggest that EMERALD, and perhaps other programs, may need to identify adolescents with anxiety and substance use and provide additional interventions from the outset.

Ginsburg A, Stadem P, Takala C, Croarkin P, et al: An examination of screening tools for collaborative care of adolescent depression. *Journal of Clinical Psychiatry* 2018; doi 10.4088/JCP.17m11543. From the Mayo Clinic, Rochester, MN. Funded by the National Center for Advancing Translational Sciences; and the NIMH. One of 8 study authors disclosed potentially relevant financial relationships; the remaining authors declared no competing interests.

*See Reference Guide.

ADHD Medications Compared

A comprehensive synthesis of clinical-trial data, based on advanced methodology for network meta-analyses, confirms methylphenidate as the preferred first choice for children and adolescents with ADHD and amphetamines as first-line therapy for adults. There is little evidence of the effects of any medication beyond 12 weeks.

Methods: The analysis was based on a wide-ranging search for studies, with no language restrictions, including dissertations, clinical-trial registries, and data on file at pharmaceutical companies. The studies were double-blind, randomized controlled trials, including parallel-group, crossover, and cluster designs, in children and adolescents (aged 5–17 years) and adults with a primary diagnosis of ADHD. The primary efficacy outcomes of the meta-analysis were change in severity of clinician-rated ADHD symptoms and change in teacher ratings, using standardized rating scales. Tolerability was assessed as the rate of treatment discontinuation. Separate analyses were conducted in children/adolescents and in adults.

Results: The search identified 133 studies, 81 in children and adolescents, 51 in adults, and 1 in patients of all ages, with a total sample size of >14,000 young people and >10,000 adults. Included studies evaluated monotherapy with any of the following medications, compared with

each other or placebo: amphetamines (including lisdexamfetamine), atomoxetine, bupropion, clonidine, guanfacine, methylphenidate (including dexamethylphenidate), and modafinil.

All medications were superior to placebo at reducing clinician-rated core ADHD symptoms in children and adolescents, with between-group standardized mean differences* of 0.62–1.02. (See table.) In all age groups, amphetamines were significantly superior to modafinil, atomoxetine, and methylphenidate. In children and adolescents, amphetamines were superior to guanfacine and methylphenidate was superior to atomoxetine. In adults, methylphenidate, atomoxetine and bupropion were superior to modafinil.

According to teacher ratings of ADHD core symptoms in children (aged ≤11 years), only methylphenidate and modafinil were superior to placebo; no data were available for amphetamines or clonidine.

Standardized Mean Differences Between Active Medication and Placebo	
Amphetamines	1.02
Bupropion	0.96
Methylphenidate	0.78
Clonidine	0.71
Guanfacine	0.67
Modafinil	0.62
Atomoxetine	0.56

Guanfacine and amphetamines had higher discontinuation rates than placebo in children and adolescents; all other drugs were at least as well tolerated as placebo. In a post-hoc analysis of individual amphetamines, only lisdexamfetamine was less well tolerated than placebo.

Discussion: Although amphetamines were the most effective agents, they were only marginally more effective than methylphenidate. While amphetamines increased diastolic blood pressure and had higher discontinuation rates, methylphenidate was the only agent found to have better tolerability than placebo. Considering both efficacy and tolerability, methylphenidate emerged as the preferred first-line treatment for ADHD in young patients.

Study Rating*—18 (100%): This study met all criteria for a systematic review and meta-analysis.

Cortese S, Adamo N, Del Giovane C, Mohr-Jensen C, et al: Comparative efficacy and tolerability of medications for attention-deficit hyperactivity disorder in children, adolescents, and adults: a systematic review and network meta-analysis. *Lancet Psychiatry* 2018; doi 10.1016/S2215-0366(18)30269-4. From the University of Southampton, U.K.; and other institutions. **Funded by the European Network for Hyperkinetic Disorders; and the U.K. National Institute for Health Research Oxford Health Biomedical Research Centre.** Of 19 study authors, 11 disclosed potentially relevant financial relationships; the remaining authors declared no competing interests.

Common Drug Trade Names: atomoxetine—*Strattera*; bupropion—*Wellbutrin*; clonidine—*Catapres*; dexamethylphenidate—*Focalin*; guanfacine—*Intuniv*, *Tenex*; lisdexamfetamine—*Vyvanse*; methylphenidate—*Ritalin*; modafinil—*Provigil*

*See Reference Guide.

Reference Guide

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.

Least Squares Mean: An average estimated from a linear model. In contrast to an arithmetic mean, which is a simple average of the values, least squares means are adjusted for other terms in the model and are less sensitive to missing data.

Odds Ratio: A comparison of the probability of an event. An odds ratio of 1 implies that the event is equally likely in both groups. An odds ratio >1 indicates that the event is more likely to occur in that group than in the comparison group.

Standardized Mean Difference: The difference between 2 normalized means; used for comparison of data obtained using different scales. A value of ≤0.2 is considered a negligible effect, 0.2–0.5 a small effect, 0.5–0.8 a medium effect, and >0.8 a large effect.

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 are posted at www.alertpubs.com.

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