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Buspirone for GAD

In children and adolescents with generalized anxiety disorder, buspirone (*BuSpar*) is well tolerated, with a similar adverse-effect profile to adults, but there is insufficient evidence to support or refute its efficacy, according to a literature review and reanalysis of data.

Background: Antidepressant treatment does not produce response in nearly 40% of youth with anxiety disorders. Medications with alternate mechanisms of action are commonly used in these patients despite limited or nonexistent safety, tolerability, and efficacy data in pediatric patients. Buspirone is approved for treatment of anxiety in adults, and case reports have suggested it may be effective in younger patients.

Methods: A literature review was conducted to identify studies of pediatric buspirone use for anxiety. Data on pharmacokinetics, safety, tolerability, and efficacy were extracted from the studies and then re-evaluated.

Results: Only 2 randomized trials in pediatric patients with GAD were found. Both were conducted nearly 2 decades ago, and the results were never published. Pharmacokinetic evaluations found a generally similar profile to adults. The efficacy trials, both multicenter U.S. studies, were similar in design, with a combined population of 558 patients, aged 6–17 years, with GAD. Participants received treatment for 6 weeks with placebo or either flexible-dose buspirone (15–60 mg/day) or buspirone in 2 fixed dosage ranges (15–30 mg/day or 45–60 mg/day). Change from baseline in the sum of the 4 anxiety items of the Kiddie Schedule for Affective Disorders and Schizophrenia for School-Age Children was the primary efficacy outcome in both trials.

The reanalysis of data from the flexible-dose trial revealed a lack of statistically significant difference between buspirone and placebo, with an effect size* of 0.14. According to a Bayesian analysis, the studies were underpowered to detect significant differences. Adverse events in the 2 studies were minimal, and lightheadedness was the only event significantly elevated relative to placebo.

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Discussion: Recently, failed and negative trials in pediatric psychiatry have been attributed to high placebo response rates. Other aspects of the FDA Modernization Act, which grants an additional 6 months of market exclusivity to drug manufacturers who investigate in children and adolescents agents already approved for use in adults, could have contributed additional biases toward inconclusive results. Furthermore, the outcome measure for the buspirone trials does not reflect the full range of symptoms or functional difficulties in young people with GAD. Because of these and other important limitations, the existing evidence base neither supports nor refutes the efficacy of buspirone for pediatric GAD; additional larger and more rigorous studies are needed.

Strawn J, Mills J, Cornwall G, Mossman S, et al: Buspirone in children and adolescents with anxiety: a review and Bayesian analysis of abandoned randomized controlled trials. *Journal of Child and Adolescent Psychopharmacology* 2018;28 (February):2–9. From the University of Cincinnati, OH; and other institutions. **Source of funding not stated. Two of 7 study authors disclosed financial relationships with commercial sources; the remaining authors declared no competing interests.**

***See Reference Guide.**

Mania: Predicting Response to Olanzapine

Early improvement is the best predictor of eventual response and remission with olanzapine (*Zyprexa*), according to a clinical trial in adolescents with manic or mixed-episode bipolar disorder.[1] This finding strengthens the case for reliance on early improvement to inform the decision of whether to switch medication.

Methods: This post-hoc analysis was conducted using data from a randomized, placebo-controlled trial of olanzapine in 161 adolescents, aged 13–17 years.[2] Participants had a diagnosis of DSM-IV-TR bipolar I disorder and were currently experiencing a manic or mixed episode, with a baseline Young Mania Rating Scale (YMRS) total score of ≥20. Those randomized to active treatment received flexible-dose olanzapine (2.5–20 mg/day) for 3 weeks. The primary efficacy outcome in the parent study was change from baseline to week 3 in the YMRS score. Early response was defined as a ≥25% reduction in YMRS score, ultimate response as a ≥50% reduction, and remission as a final score of ≤12 (standard definition) or ≤8 (stringent definition). For the present analysis, potential predictors of ultimate response and remission were evaluated.

Results: Study participants had a mean age of 15 years and had illness onset a mean of 3 years previously. A total of 72 patients (69%) met criteria for early response to olanzapine. These early responders were more likely to have mixed episodes than early nonresponders, had higher baseline scores on the YMRS items for sleep and thought content, and received lower doses of olanzapine during double-blind treatment.

Early response was strongly predictive of ultimate response and remission. (See table.) Early responders also had greater average reductions in YMRS total score, as well as greater improvement on secondary outcome measures including the Clinical Global Impression Severity and Improvement scales and the Overt Aggression Scale.

Early response vs nonresponse as predictor of ultimate treatment outcomes

Outcome	Early responders (n=72)	Early nonresponders (n=32)	Significance
Ultimate response	44 (61%)	7 (22%)	p<0.001
Standard remission (YMRS ≤12)	33 (46%)	4 (12.5%)	p<0.001
Stringent remission (YMRS ≤8)	24 (33%)	1 (3%)	p<0.001
Mean change in YMRS total score	-56.4%	-29.8%	p<0.001

Statistical calculations identified an optimal cutoff point of a 35.5% reduction in YMRS score during week 1 as having the greatest accuracy in predicting ultimate response, with both a sensitivity and specificity* of about 70%. A cutoff of a 39% YMRS reduction at week 1 was the most accurate predictor of remission. In a multivariate analysis, early response was the strongest predictor of ultimate response; other significant predictors for individual outcomes included schizophrenia in a second-degree relative, fewer previous psychiatric hospitalizations, and male gender. Most adverse effects did not differ between early responders and nonresponders.

Discussion: These observations suggest initial treatment of mania should be reevaluated in patients who do not show substantial improvement within the first week. A 35% decrease in symptom score appear to be an appropriate threshold to gauge early improvement.

[1]Xiao L, Ganocy S, Findling R, Chang K, et al: Baseline characteristics and early response at week 1 predict treatment outcome in adolescents with bipolar manic or mixed episode treated with olanzapine: results from a 3-week, randomized, placebo-controlled trial. *Journal of Clinical Psychiatry* 2017; doi 10.4088/JCP.16m10923. From Capital Medical University, Beijing, China; and other institutions. **Funded by Eli Lilly and Company. Six of 9 study authors disclosed financial relationships with commercial sources; the remaining authors declared no competing interests.**

[2]Tohen M, et al: Olanzapine versus placebo in the treatment of adolescents with bipolar mania. *American Journal of Psychiatry* 2007;164:1547–1556.

***See Reference Guide.**

Predictors and Moderators of Depression Relapse

In an analysis of clinical-trial data, children and adolescents whose depression was successfully treated with fluoxetine (*Prozac*) had an increased risk of relapse if they had comorbid dysthymia at baseline and higher levels of residual symptoms after acute treatment.[1] Relapse rates were also higher in girls than in boys.

Methods: This secondary analysis was based on a clinical trial of continuation therapy with fluoxetine.[2] Study participants, aged 7–18 years, had a ≥4-week history of major depressive disorder of at least moderate severity. Response was assessed after 12 weeks of treatment with open-label fluoxetine and was defined as a reduction of ≥50% in the Children's Depression Rating Scale–Revised (CDRS-R) score and a Clinical Global Impression–Improvement rating of much improved or better. Patients who met response criteria were randomly assigned to an additional 6 months of continued fluoxetine or a switch to placebo. Relapse was defined as a CDRS-R total score of ≥40. Potential predictors and mediators of relapse were chosen based on the findings of recent large-scale studies of depression treatment in young patients. Both predictors and moderators are present before treatment; predictors influence outcomes regardless of treatment type, while moderators affect the outcome differently depending on treatment.

Results: Of 168 patients who received fluoxetine, 102 met response criteria and were randomly assigned to continued fluoxetine or placebo. Patients had a mean age of 11.5 years, and slightly more than half were boys. Relapse occurred during the 6-month extension period in 36 study participants and was less common with fluoxetine than with placebo (22% vs 48%; p=0.007).

No baseline demographic or illness characteristics were predictive of relapse. Relapse was predicted by comorbid dysthymia at baseline and by both child and parent perception of poor leadership in the family. Odds of relapsing were also increased in patients with higher depression scores or with residual sleep disturbance after acute treatment.

Gender was a moderator of relapse in fluoxetine-treated patients only, with a nearly 9-fold greater risk of relapse in girls than in boys who continued the drug. (See table, next page). Boys who received fluoxetine had a much lower risk of relapse than those who received placebo.

A higher average CDRS-R score at randomization predicted a higher likelihood of relapse in patients who received fluoxetine, but not placebo. Among patients with no residual insomnia at week 12, the odds of relapsing were significantly lower with fluoxetine than placebo. Comorbid dysthymia, family leadership, and residual irritability were not moderators of the relationship between treatment and relapse prevention.

Predictors and moderators of treatment relapse in multiple regression models

Predictors	Odds ratio*	Significance
Comorbid dysthymia	2.88	p=0.03
Perception of poor family leadership Child score Parent score	 1.39 1.24	 p=0.006 p=0.05
Week 12 depression severity (CDRS-R)	1.21	p=0.003
Week 12 residual insomnia	6.74	p=0.006
Moderators in fluoxetine-treated patients	**Odds ratio**	**Significance**
Female vs male	8.86	p=0.007
Baseline CDRS-R total score±	1.14	p=0.03
Anxiety score at randomization	0.19	p=0.002
No residual insomnia	0.12	p=0.006

Odds ratios are adjusted for treatment (fluoxetine vs placebo), age, gender, and CDRS-R at start of continuation treatment.
±Odds of relapse were multiplied by 1.14 (i.e., 14% higher) for every 1-unit increase in the CDRS-R score.

Discussion: Current guidelines recommend continuing medication for 6–9 months after response to an antidepressant. Nevertheless, relapse rates are still high. The present study has identified some factors that could help identify patients who would benefit from additional psychoeducation and treatment tailored to their specific risk factors. The results of the moderator analysis are difficult to interpret because moderator analyses generally require a larger sample size, and the findings regarding placebo are not relevant to real-world practice.

[1]Kennard B, Mayes T, Chahal Z, Nakonezny P, et al: Predictors and moderators of relapse in children and adolescents with major depressive disorder. *Journal of Clinical Psychiatry* 2018; doi 10.4088/JCP.15m10330. From the University of Texas Southwestern Medical Center and Children's Medical Center, Dallas. **Funded by the NIMH. One of 6 study authors disclosed financial relationships with commercial sources; the remaining authors declared no competing interests.**

[2]Emslie G, et al: Fluoxetine versus placebo in preventing relapse of major depression in children and adolescents. *American Journal of Psychiatry* 2008;165:459–467. See *Child & Adolescent Psychiatry Alerts* 2008;10 (April):21.

***See Reference Guide.**

Gene-Targeted Therapy in ADHD

Fasoracetam, a metabotropic glutamate receptor (mGluR) activator, was well tolerated and showed preliminary evidence of efficacy in adolescents with ADHD who had variants in mGluR network genes.

Background: Copy number variants (CNVs) in the mGluR gene network occur in an estimated 11% of children with ADHD, about 10-times the frequency in unaffected children. Fasoracetam is an investigational drug that has undergone clinical trials for vascular dementia and has been shown to reverse induced memory and learning deficits in animal models.

Methods: The present phase I trial was conducted in 30 patients, aged 12–17 years, with a diagnosis of ADHD who had been screened for mGluR mutations in a large-scale genomic study. After a washout of previous medications, participants underwent 24-hour pharmacokinetic testing. Afterward, all participants received single-blind placebo for 1 week, followed by

fasoracetam in weekly escalating dosages of 50, 100, 200, and 400 mg b.i.d. Efficacy was measured using the Clinical Global Impression (CGI) Improvement and Severity scales,* the Vanderbilt Parent Scale, and the parental Behavior Rating Inventory of Executive Function (BRIEF).

Results: Patients showed clinical improvement on all 4 efficacy measures during each week of active treatment. The strongest improvements were in the CGI-I score, which decreased from a mean of 3.8 during the placebo week to 2.3 during the final week of treatment. The mean CGI-S score decreased from 4.9 to 3.93. Significant improvement did not occur until the second active treatment week, which suggests a minimum dosage of 100 mg b.i.d. may be required to observe a benefit. Improvements in the Vanderbilt and BRIEF measurements were less pronounced than those in the CGI scales.

In an additional analysis, patients were stratified into 3 tiers according to specific mGluR variants. The 2 highest-risk tiers had significantly larger CGI-I and CGI-S responses than the group with less severe mutations. Actigraphy monitoring, performed throughout the study, showed that adolescents had a net reduction of moderate-to-high intensity and repetitive movements between the placebo week and the highest-dosage week. Adverse events were mild and occurred at similar rates during placebo and drug administration.

Discussion: Although preliminary, these study results support the continued investigation of fasoracetam as a treatment for ADHD. They also highlight the value of genetic prioritization and targeted therapy in ADHD.

Elia J, Ungal G, Kao C, Ambrosini A, et al: Fasoracetam in adolescents with ADHD and glutamatergic gene network variants disrupting mGluR neurotransmitter signaling. *Nature Communications* 2018; doi 10.1038/s41467-017-02244-2. From Nemours/Alfred I. du Pont Hospital for Children, Wilmington, DE; and other institutions. **Funded by neuroFix Therapeutics Inc. One of 24 study authors disclosed financial relationships with commercial sources; the remaining authors declared no competing interests.**

***See Reference Guide.**

Mixed-Release Amphetamine

The newly-approved triple-bead mixed amphetamine salts SHP465 (*Mydayis*) was effective and well tolerated in a clinical trial in children and adolescents. The new formulation contains 3 types of drug-releasing beads, providing immediate and delayed release at pH values of 5.5 and 7.

Methods: Study participants, recruited from 36 U.S. sites, were aged 6–17 years and had a primary diagnosis of DSM-IV-TR ADHD, with a baseline ADHD Rating Scale-IV (ADHD-RS-IV) score of ≥28. After a washout of previous medications, patients were randomly assigned to receive double-blind treatment with 12.5 mg SHP465 or placebo, taken once daily at 7AM. At the end of the first study week, the dose was increased to 25 mg based on response and tolerability. The primary efficacy outcome, assessed after 4 weeks, was change from baseline in the ADHD-RS-IV total score. The 4-week score on the Clinical Global Impression–Improvement* scale was the key secondary endpoint.

Results: Of 264 enrolled patients, about 40% were aged ≤12 years, and 234 completed the study. The most frequent reasons for withdrawal were adverse events (11 patients receiving SHP465 and 3 receiving placebo) and lack of efficacy (1 with SHP465, 4 with placebo). The optimal daily dose of SHP465 was 25 mg in 72% of patients and 12.5 mg in 24%.

At baseline, the mean total ADHD-RS-IV scores were 39 and 40 in the SHP465 and placebo groups, respectively. At the 4-week assessment, scores were reduced by 21 points with SHP465, compared with 11 points with placebo (effect size,* 0.80; $p<0.001$). Scores on both

the hyperactivity/impulsivity and inattentiveness subscales decreased to a significantly larger extent with SHP465 than placebo ($p<0.001$ for both). The mean CGI-I score at week 4 was 3 for placebo and 2.2 for SHP465 (effect size, 0.65; $p<0.001$).

The most frequently reported adverse events with SHP465 were decreased appetite and insomnia. Of the adverse events that led to study discontinuation, 9 were related to the study drug. All were of mild or moderate severity and resolved with treatment discontinuation.

Discussion: Previously published studies have shown that SHP465 is safe and efficacious in adults. This is the first published phase III study in children and adolescents; the agent is approved for use in patients aged ≥13 years. Although efficacy cannot be compared directly, the effects of SHP465 appear similar to other long-acting stimulants. The adverse-effect profile is also consistent with other long-acting amphetamines.

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

Brams M, Childress A, Greenbaum M, Yu M, et al: SHP465 mixed amphetamine salts in the treatment of attention-deficit/hyperactivity disorder in children and adolescents: results of a randomized, double-blind placebo-controlled study. *Journal of Child and Adolescent Psychopharmacology* 2018;28 (January):19–28. From Baylor College of Medicine, Houston, TX; and other institutions including Shire, Lexington, MA. **Funded by Shire Development, LLC. All study authors disclosed financial relationships with commercial sources including Shire.**

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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.

Clinical Global Impression–Severity (CGI-S) Scale: A 7-point rating of the severity of illness. A score of 1 corresponds to a rating of normal; 2=borderline mentally ill; 3=mildly ill; 4=moderately ill; 5=markedly ill; 6=severely ill; 7=extremely ill.

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.

Odds Ratio: A comparison of the probability of an event in 2 groups. An odds ratio of 1 implies that the event is equally likely in both groups. An odds ratio greater than 1 indicates that the event is more likely to occur in that group than in the comparison group.

Sensitivity and Specificity: Statistical measures of the performance of binary classification tests. Sensitivity measures the proportion of actual positives that are correctly identified (i.e., the percentage of sick people who are correctly identified as having the condition). Specificity measures the proportion of negatives that are correctly identified (i.e., the percentage of healthy people who are correctly identified as not having the condition). A perfect predictor would have 100% sensitivity and specificity.

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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