Guanfacine for Functional Impairment in ADHD

According to a secondary analysis of data from a randomized placebo-controlled trial, once-daily extended-release guanfacine (Intuniv) improves functional impairment in children and adolescents with ADHD.

**Methods:** Study subjects, aged 6–12 years (mean age, 9 years), had a primary diagnosis of ADHD and ADHD Rating Scale–IV and Clinical Global Impression–Severity scores indicating at least moderate severity. Participants were randomly assigned to either placebo or to extended-release guanfacine, administered as a single dose in the morning or evening (because the study was not powered to test the difference between morning and evening dosing, the groups were pooled for analysis). The guanfacine dose was optimized over the first 5 weeks of the study and held stable over the remaining 3 weeks. Functional impairment was measured at baseline and at weeks 5 and 8 using the Weiss Functional Impairment Rating Scale–Parent Report (WFIRS-P), a brief rating scale developed specifically for children and adolescents with ADHD that consists of 50 items in 6 domains. A total of 221 patients received guanfacine, and 112 received placebo.

**Results:** Patients who received guanfacine had significantly larger improvement in WFIRS-P total score than those who received placebo (effect size,* 0.45; p<0.001). Among the 6 domains, guanfacine was associated with improvement in Family, Learning and School (including the subdomains of Academic Performance and Behavior in School), Social Activities, and Risky Activities, with effect sizes ranging from about 0.3 to 0.5 and p values usually <0.001. Two domains, Life Skills and Self-Concept, were unaffected by guanfacine treatment. Patients whose ADHD symptoms were responsive to guanfacine or placebo also showed more robust responses in measures of function.

**Discussion:** Clinical trials of ADHD treatment have largely focused on symptoms of the disorder, but this study and others suggest that treatment benefits may also extend to functional outcomes. In this study, effect sizes for functional domains were in the moderate range.

---

* Did you know you can earn more CME credit with our other publications? See back page for details.
and slightly lower than those observed for ADHD symptoms. The lack of improvement in Life Skills and Self-Concept suggests that these domains may require more intensive or longer treatment.

Stein M, Sikirica V, Weiss M, Robertson B, et al: Does guanfacine extended release impact functional impairment in children with attention-deficit/hyperactivity disorder? Results from a randomized controlled trial. CNS Drugs 2015; doi: 10.1007/s40263-015-0291-6. From Seattle Children’s Hospital, WA; and other institutions including GlaxoSmithKline, King of Prussia, PA. Funded by Shire Development, LLC. All 6 study authors disclosed financial relationships with commercial sources.

*See Reference Guide.

Bright Light Therapy for Adolescent Depression

A 2-week course of adjunctive bright light therapy was feasible and acceptable in adolescent inpatients with moderate-to-severe depression. Both bright light and the control treatment were associated with improvement in depression.

Methods: Study participants were medication-naïve, aged 12–18 years, and admitted to a German pediatric psychiatric hospital with a primary diagnosis of moderate-to-severe depression. All patients received standard multimodal psychological treatments including: individual and group psychotherapy; nursing and medical care; school; occupational therapy; family therapy; and other interventions. Afternoon outdoor activities were also part of standard treatment. In addition to the standard treatment, study participants were randomly assigned to receive either bright light therapy (10,000 lux) or inactive dim light (≤150 lux) about 1 week after admission. Both treatments consisted of 45 minutes of morning light exposure 5 times a week for 2 weeks. Multiple outcomes were assessed immediately post treatment and after 3 weeks of follow-up: depression with the Beck Depression Inventory-II (BDI-II), sleep with the German sleep questionnaire SFB/R, and chronotype with the Morning-Evening Questionnaire.

Results: A total of 57 patients received study treatment. Seven patients discontinued the intervention, and 9 others were lost to follow-up by week 3; all were included in the outcome analysis. Baseline depression was moderate in 34 patients and severe in 23; about one-third had a seasonal pattern of depression.

Both treatment groups showed significant improvement in depression according to BDI-II scores (p<0.001), with no difference between the groups. Rates of remission (i.e., BDI-II score <10) after treatment were 20% with bright light therapy and 11% for controls, a nonsignificant difference. Remission rates at 3 weeks were 47% and 26%, respectively (p=0.09).

Sleep quality and the amount of restorative sleep improved during treatment in the bright light therapy group, but not in the comparison group (p=0.007 and p<0.001, respectively). The control group showed some improvement in sleep quality only between the end of treatment and follow-up. Sleep quality was at least markedly improved in 27% of the bright light therapy group, compared with 7% of controls (p=0.03). Both groups showed continued improvement over follow-up. Short-term remission/improvement in restorative sleep occurred in 50% and 15% of patients, respectively (p=0.002). Shifts toward a "morningness" chronotype occurred earlier and more often in the group receiving bright light therapy. Enhanced sleep quality and chronotype shifts were predictive of greater improvement in depression, while bright light therapy and restorative sleep changes were not.

Discussion: The study interventions were feasible and accepted by both patients and hospital staff. The study may have failed to show superiority of bright light therapy because of a high placebo response rate, the therapeutic effects of other elements of the treatment protocol,
small sample size, and an insufficient observation period. It is likely that improvements in sleep and a shift toward morningness may require more than a few weeks to show antidepressant effects; additional study appears to be warranted.

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

Bogen S, Legenbauer T, Gest S, Holtmann M: Lighting the mood of depressed youth: feasibility and efficacy of a 2 week-placebo controlled bright light treatment for juvenile inpatients. *Journal of Affective Disorders* 2016;190 (January):450-456. From the LWL University Hospital of the Ruhr University Bochum, Hamm, Germany. Funded by the LWL-Research Institute for Mental Health and Prevention, Bochum, Germany. The authors did not include disclosure of potential conflicts of interest.

*See Reference Guide.*

### Fatty Acids plus Inositol for Bipolar Spectrum Disorders

In a pilot study, the combination of omega-3 fatty acids and inositol was more effective than either agent alone at reducing symptoms of bipolar disorder in children. The study treatments, which were largely free of adverse effects, may be promising as alternative or augmenting therapy.

**Methods:** Study participants (n=24) were children, aged 5–12 years, with a diagnosed bipolar spectrum disorder who were experiencing manic symptoms of mild-to-moderate severity but no major delusions or hallucinations. Participants could be experiencing manic, hypomanic, or mixed symptoms when randomized. With the exception of ADHD treatments, concomitant CNS medications were not permitted during the study. Patients were not required to be treatment-naive, and those with a poor response to their pre-study medications could discontinue them and undergo randomization. Following baseline assessment, children were randomly assigned in double-blind fashion to 12 weeks of 1 of 3 treatments: inositol plus placebo, high-eicosapentaenoic acid (EPA) omega-3 fatty acids plus placebo, or the combination of both active supplements. Double-placebo treatment was not deemed ethical. High-EPA omega-3 fatty acid was given as 6 capsules per day of a commercially available supplement with 325 mg EPA and 225 mg docosahexaenoic acid (DHA) per 2 capsules. Inositol capsules were compounded for the study and dosed at 4 daily 500-mg capsules for children weighing ≥55 lbs. and 80 mg/kg for smaller children. Outcome measures included the Young Mania Rating Scale (YMRS), Brief Psychiatric Rating Scale (BPRS), Children's Depression Rating Scale (CDRS), and Clinical Global Impression–Improvement (CGI-I) scale.

**Results:** A total of 11 patients dropped out of treatment—7 for lack of efficacy and 4 because of poor or non-compliance—but were included in the intent-to-treat analysis. All treatments, and particularly combined treatment, were associated with improvement from baseline in bipolar disorder symptoms. (See table, next page). Combined treatment was generally associated with a higher likelihood of favorable outcomes than the other treatments. Response, defined as a ≥30% decrease in YMRS score, occurred more often with combined treatment than either monotherapy (odds ratios* for combined treatment vs. inositol and fatty-acid monotherapies, 1.13 and 3.75, respectively). CGI-I scale ratings of much improved or better also occurred more frequently with combined treatment (odds ratio vs. inositol and fatty-acid monotherapies, 3.11 and 5.83, respectively). Euthymia, defined as a final YMRS score of <12, was also more likely with combined treatment (odds ratio vs. inositol and fatty-acid monotherapies, 7.0 and 1.07, respectively).

Patients experienced few adverse events other than gastrointestinal symptoms. The treatments had no effect on weight or cardiovascular parameters, except for a mean 15-point drop in diastolic blood pressure in the inositol monotherapy group.
Discussion: These study results confirm previous observations with omega-3 fatty acids, while the improvement with inositol is a novel finding. The 2 treatments have complementary mechanisms: Omega-3 fatty acids increase membrane fluidity, and inositol acts as a second messenger in multiple neurotransmitter systems. Effect sizes in this study were generally large, although interpretation is limited by small sample size.

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


*See Reference Guide.

Treating Subsyndromal Bipolar Disorder

In a pilot study of children with subsyndromal bipolar disorder, individual family psychoeducational psychotherapy (IF-PEP), alone and in combination with omega-3 fatty acids, was acceptable and improved depressive symptoms.

Background: Subsyndromal presentations of bipolar disorder—NOS and cyclothymia—are highly impairing but have no evidence-based treatment guidelines. Nonpharmacologic interventions may have a more favorable risk–benefit profile in subsyndromal patients than currently available drugs.

Methods: Study participants were aged 7–14 years and had a confirmed diagnosis of bipolar disorder NOS or cyclothymia. Those with active suicidal ideation were excluded. Study patients were randomly assigned to 1 of 4 treatment groups: IF-PEP with omega-3 supplementation, IF-PEP with placebo supplementation, omega-3 supplementation plus active monitoring (placebo condition for IF-PEP), or placebo supplementation plus active monitoring. IF-PEP was delivered in 2 weekly sessions (1 parent-only and 1 child–parent), each typically lasting about 45–50 minutes. The treatment was manualized and included workbooks, activity worksheets, and between-session homework. The program included information about the disorder, symptom management, healthy habits, problem-solving skills, and communication skills. Active monitoring consisted of 5 assessments lasting about 90 minutes. Omega-3 fatty acids were provided as 2 capsules twice daily, each containing 350 mg EPA, 50 mg DHA, and 100 mg other omega-3 fatty acids. The study investigated a range of outcomes rated with the Depression and Mania subscales of the Kiddie Schedule for Affective Disorders

<table>
<thead>
<tr>
<th>Measure</th>
<th>Inositol Monotherapy</th>
<th>Omega-3 Fatty Acid Monotherapy</th>
<th>Combined Inositol–Fatty Acids</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Baseline</td>
<td>End Point</td>
<td>Effect Size*</td>
</tr>
<tr>
<td>YMRS</td>
<td>25</td>
<td>18</td>
<td>1.47</td>
</tr>
<tr>
<td>CDRS</td>
<td>44</td>
<td>37</td>
<td>0.84</td>
</tr>
<tr>
<td>BPRS</td>
<td>46</td>
<td>44</td>
<td>0.21</td>
</tr>
</tbody>
</table>

Change from baseline in measures of mania, general psychopathology, and depression
and Schizophrenia (KDRS and KMRS, respectively); the Children’s Depression Rating Scale-Revised (CDRS-R); and the Young Mania Rating Scale (YMRS).

**Results:** A total of 23 children participated in the study. All patients had comorbidity, with anxiety, ADHD, and disruptive behavior disorders each affecting ≥ 65%. Adherence to study medication was ≥ 89%. Families assigned to IF-PEP completed an average of nearly 16 of the 17 planned sessions. All patients completed ≥ 4 weeks of study treatment, and 83% completed the 12-week trial.

Patients randomly assigned to combined therapy had significantly greater improvement in depression measured with the KDRS than the double-control group (effect size, *1.70; p=0.01) and the omega-3-only group (effect size, 0.48). Treatment did not differentially affect CDRS-R-rated depression. Manic symptoms declined in all groups, but there were no significant treatment-related differences. Neither monotherapy was significantly superior to combined treatment on any outcome measure, but omega-3 monotherapy had a large effect (0.86) on the YMRS, and IF-PEP monotherapy had a large effect on the KDRS (0.92). Combined therapy was not superior to IF-PEP monotherapy for any outcome.

**Discussion:** Mainly because of the small sample size, the conclusions that can be drawn from this research are limited. However, compared with available pharmacotherapies, both fatty acid supplementation and IF-PEP have a favorable risk–benefit profile and additional, more rigorous study appears to be warranted.

Fristad M, Young A, Vesco A, Nader E, et al: A randomized controlled trial of individual family psychoeducational psychotherapy and omega-3 fatty acids in youth with subsyndromal bipolar disorder. *Journal of Child and Adolescent Psychopharmacology* 2015;25 (December):764–774. From The Ohio State University, Columbus; and Children’s Hospital of Eastern Ontario, Ottawa, Canada. Funded by the NIMH; and the National Center for Research Resources. Two study authors disclosed financial relationships with commercial sources; the remaining 6 authors declared no competing interests.

*See Reference Guide.*

**Cannabis, Brain Maturation, and Schizophrenia**

In a population-based study, cannabis use in early adolescence was associated with reduced cortical thickness in boys at high genetic risk for schizophrenia. Cannabis-associated changes in brain structure were not found in boys with low genetic risk scores or in girls.

**Methods:** Study subjects (n=1577) included 3 separate population-based samples of adolescents: 1 Canadian sample assessed at a single time in a cross-sectional manner, and 2 European samples (1 all male, 1 mixed-gender) studied longitudinally through adolescence. All adolescents had marijuana use ascertained, underwent brain MRI imaging between the ages of 14 and 21 years, and had genetic risk for schizophrenia evaluated using a polygenic risk score based on 108 loci identified by the Psychiatric Genomics Consortium. The primary outcome variable was mean cortical thickness, a proxy for the effects of various exposures on cortical neurobiological features, especially certain cell types and capillary densities. The primary exposure of interest was cannabis use before age 16 years. The genetic risk score was explored as a possible mediator of this relationship.

**Results:** In the Canadian sample, age-adjusted cortical thickness decreased significantly with increasing schizophrenia genetic risk scores in male cannabis users (p=0.009), but not in non-users of any gender and just slightly in girls. In the all-male European sample, a significant association was found between reduced cortical thickness and the highest frequency of prior cannabis use (≥ 61 occasions before age 16 years; p=0.02) in the adolescents with genetic risk scores above the median. No relationship was demonstrated in young men with low genetic risk. In the other European sample, any cannabis use before
age 16 years, versus no use, and the genetic risk score had an interactive effect on longitudinal changes in cortical thickness. In girls, genetic risk was associated with reduced cortical thickness, but cannabis use did not contribute to this effect. In all 3 population samples, the largest effects of cannabis were found in brain regions with the highest expression of the cannabinoid receptor 1 gene.

**Discussion:** Two processes might underlie brain thinning in adolescent males at risk of schizophrenia: interference with experience-related brain plasticity and testosterone-driven perturbations of cortical maturation. Cannabis exposure may accelerate these processes.

French L, Gray C, Leonard G, Perron M, et al: Early cannabis use, polygenic risk score for schizophrenia, and brain maturation in adolescence. *JAMA Psychiatry* 2015;72 (October):1002–1011. From the Rotman Research Institute, Toronto, Canada; and other institutions. **Funded by the Canadian Institutes of Health Research; and other sources. One study author disclosed financial relationships with commercial sources; the remaining 37 authors declared no competing interests.**

**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.

**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.

**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.

**DID YOU KNOW?**

You can earn up to 72 credits per year* by enrolling in all 3 of our CME programs.

*Child & Adolescent Psychiatry Alerts
*Psychiatry Drug Alerts
*Psychiatry Alerts NOS

Call today (973-898-1200) or visit www.alertpubs.com/continuing-education.html to enroll.

* M.J. Powers & Co. Publishers is accredited by the Accreditation Council for Continuing Medical Education to provide continuing medical education for physicians.

Contributing Editors: Kate Casano, MSHyg  Bennett Silver, MD
Consulting Editor: Theodore A. Petti, MD, Rutgers–Robert Wood Johnson Medical School
Executive Editor: Trish Elliott  Associate Editor: Tara Hausmann  Assistant Editor: Kasey Madara
Founding Editor: Michael J. Powers

Statement of Editorial Policy: All of the information and opinions presented in each *Child & Adolescent Psychiatry Alerts* article are strictly those contained in the cited article unless otherwise noted. Reader comments are welcome by mail, by telephone (973-898-1200) 9:00AM–3:00PM Eastern time Monday–Friday, or by e-mail (child@alertpubs.com).