Comparative Efficacy of ADHD Treatments

According to the results of a manufacturer-sponsored network meta-analysis,* lisdexamfetamine appears to be the most effective among agents approved in the U.K. for treatment of ADHD in children and adolescents, while immediate-release (IR) methylphenidate appears to have the best tolerability.

**Methods:** A comprehensive literature search was undertaken to identify randomized controlled trials of dextroamphetamine, atomoxetine, IR clonidine, IR or extended release (ER) guanfacine, lisdexamfetamine, or IR or ER/OROS methylphenidate for treatment of ADHD in patients aged 6–17 years. Studies were included in the network meta-analysis if treatment duration was ≤16 weeks and the study drug could be connected to either of the nonstimulants by a chain of common comparators. Efficacy outcomes, which differed by study, included change in total ADHD Rating Scale-IV (ADHD-RS-IV) total score and Clinical Global Impression–Improvement (CGI-I) response, defined as a rating of much improved or very much improved. Safety endpoints included discontinuation for any reason and for adverse effects.

**Results:** A total of 36 studies met inclusion criteria; of these, 20 evaluated ADHD-RS-IV change, 14 evaluated CGI-I response, 31 reported all-cause discontinuation, and 32 reported discontinuation due to adverse effects. Study durations ranged from 3 to 16 weeks, and treatment arms included 16–222 subjects. Mean baseline ADHD-RS-IV scores, available from 22 studies, ranged from 31.5 to 43.5. Data was insufficient to include dextroamphetamine, clonidine, and IR guanfacine in the network analysis.

Efficacy of lisdexamfetamine was superior to all other treatments when measured using either ADHD-RS-IV or CGI-I change. (See table, next page.) The calculated probability of lisdexamfetamine being the most effective pharmacotherapy was 99.96% for ADHD-RS-IV change and 96.21 for CGI-I response. When only nonstimulants were considered, ER guanfacine was superior to atomoxetine for both efficacy outcomes. Among the agents, IR methylphenidate was the best tolerated, with the lowest rates of both all-cause discontinuation and adverse
effect-related discontinuation. However, sample sizes for safety outcomes were small and statistical uncertainty was high. Of the nonstimulants, atomoxetine was less likely than guanfacine to be discontinued. (See table.)

<table>
<thead>
<tr>
<th>Efficacy</th>
<th>ADHD-RS-IV Score: Decrease from Baseline Relative to Placebo</th>
<th>Odds Ratio* for CGI-I Response vs Placebo</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lisdexamfetamine</td>
<td>14.98</td>
<td>8.43</td>
</tr>
<tr>
<td>ER Methylphenidate</td>
<td>9.33</td>
<td>4.27</td>
</tr>
<tr>
<td>ER Guanfacine</td>
<td>8.68</td>
<td>3.34</td>
</tr>
<tr>
<td>Atomoxetine</td>
<td>6.88</td>
<td>2.69</td>
</tr>
<tr>
<td>IR Methylphenidate</td>
<td>Not evaluated</td>
<td>2.22</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Safety</th>
<th>Relative Risk* for All-Cause Discontinuation</th>
<th>Relative Risk for Adverse Effect Discontinuation</th>
</tr>
</thead>
<tbody>
<tr>
<td>IR Methylphenidate</td>
<td>0.44</td>
<td>1.20</td>
</tr>
<tr>
<td>ER Methylphenidate</td>
<td>0.52</td>
<td>1.38</td>
</tr>
<tr>
<td>Lisdexamfetamine</td>
<td>0.66</td>
<td>3.11</td>
</tr>
<tr>
<td>ER Guanfacine</td>
<td>0.87</td>
<td>4.49</td>
</tr>
<tr>
<td>Atomoxetine</td>
<td>0.88</td>
<td>2.39</td>
</tr>
</tbody>
</table>

**Discussion:** While these results suggest lisdexamfetamine is the most effective agent and IR methylphenidate the best tolerated, the clinical implications are limited because no risk–benefit assessment was conducted in the study. This type of comparison would be useful to better inform clinical practice.

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

Joseph A, Ayyagari R, Xie M, Cai S, et al: Comparative efficacy and safety of attention-deficit/hyperactivity disorder pharmacotherapies, including guanfacine extended release: a mixed treatment comparison. European Child and Adolescent Psychiatry 2016; doi 10.1007/s00787-017-0962-6. From Shire, Switzerland and Wayne, PA; and other institutions. **Funded by Shire. All study authors disclosed financial relationships with commercial sources.**

**Common Drug Trade Names:** atomoxetine—Strattera; clonidine—Catapres; dexamphetamine—Dexedrine; ER guanfacine—Intuniv; IR guanfacine—Tenex; lisdexamfetamine—Vyvanse; ER/ÖROS methylphenidate—Concerta; IR methylphenidate—Ritalin

*See Reference Guide.

**CBT for Selective Mutism**

In a pilot study, the brief family-based cognitive-behavioral intervention Social Communication Anxiety Treatment (S-CAT) improved children’s selective mutism and the accompanying anxiety and social withdrawal.

**Methods:** Study families (n=40) had contacted a specialty practice for selective mutism to take advantage of a grant-funded, free-of-charge treatment. All children (mean age, 7 years) had a prior diagnosis of selective mutism, which was confirmed by treating clinicians based on DSM-IV or DSM-5 criteria and scores on several standardized symptom questionnaires. The primary outcome measure was the Selective Mutism Questionnaire (SMQ), a 17-item parent questionnaire that rates the child’s frequency of speaking, with subscales for at school, at home, and in public or social situations. S-CAT was delivered in 3 sessions, once every 3 weeks, with guided homework in between. Important elements of the treatment include the therapist’s “nonchalant” technique, with low pressure on the child to speak; reducing parents’
enabling behaviors and children's avoidance behaviors; and using behavioral and cognitive strategies to help children communicate in increasingly challenging situations. Children were evaluated before each therapy session and at the final follow-up at week 15 (6 weeks after the last office session). A complete description of S-CAT therapy is available at www.selectivemutismcenter.org/aboutus/SelectiveMutism.Treatment.ShiponBlum.

Results: The 33 children who completed study treatment showed a significant increase in speech after the first 3 weeks and continued to improve throughout the study and follow-up. At the 15-week follow-up, children demonstrated statistically significant improvement in speaking frequency, as measured with the SMQ total score and the family, school, and public/social subscales (p<0.001 for linear trend for each outcome). Among individual items on the SMQ, the largest gains were in social situations outside of school, such as speaking with store clerks or unknown children. Even at home, where children were already speaking, the frequency of speech with family friends and babysitters doubled. Larger gains were associated with family compliance and with lower initial symptom severity. Children also showed reduced parent-rated anxiety and withdrawal, according to the Child Behavior Checklist.

Discussion: There have been many published studies of selective mutism treatment, but most are single-case reports. The few more rigorous studies have suggested cognitive-behavioral approaches are promising. Among these, S-CAT may be particularly effective because activities are guided by the child's comfort level, the therapist minimizes expectations and pressure to speak, parents are heavily involved, and motivation is an important element of treatment.


Cognitive Control Deficits and Suicide Risk

In a group of hospitalized adolescents, deficits in cognitive control were associated with a history of suicide attempts. These deficits may be a useful addition to suicide risk assessment because they do not depend on potentially unreliable patient report.

Background: Cognitive control refers to the ability to adapt attention, thoughts, or behavior to facilitate an internal goal. In the Suicide Stroop Task (SST), used in this study to measure cognitive deficits, subjects are shown words and asked to name the ink color. The content of each word may be either suicide-related or emotionally positive, negative, or neutral. Difference in reaction times between individual word categories indicates interference, and increased interference reflects cognitive control deficits. Adults with suicidality have been shown to have increased interference with suicide-related words, but this appears to be the first study of cognitive control using the SST in adolescents with suicidality.

Methods: Adolescents who reported suicidal ideation on ≥1 day during the previous week were recruited within 48 hours of admission to a short-term inpatient treatment program. A total of 98 patients (aged 13–18 years; 71 girls) were eligible and agreed to participate in the study. The group included 60 adolescents with only suicidal ideation and 38 with ≥1 lifetime suicide attempt, of whom 26 had multiple attempts. Each participant had 48 trials of the SST, with an equal number of randomly-ordered words that were positive, negative, neutral, and suicide-related. Only correct responses (i.e., correct color identification) were included in the analysis.
Results: Total reaction times and number of errors did not differ significantly across groups. In addition, the groups did not differ in terms of negative or neutral interference. However, patterns did emerge in terms of suicidal and positive interference.

Suicidal term-related interference. In patients who had attempted suicide, interference from suicide-related terms was significantly greater than in those with suicidal ideation (p=0.044; effect size,* 0.41). Multiple attempters had even greater interference than those with only ideation (p=0.004; effect size, 0.64). No significant differences were found between single and multiple attempters or between single attempters and ideators.

Positive term-related interference. Suicide attempters also had greater interference from positive words than did those with suicidal ideation (p=0.01; effect size, 0.53). Again, effects were larger for adolescents with multiple attempts than ideators (p<0.001; effect size, 0.79) and for multiple versus single attempters (p=0.03; effect size, 0.76). Only interference from positive emotional stimuli was associated with the recency of a suicide attempt.

Discussion: One-third of adolescents with suicidal ideation transition to a suicide attempt. This study suggests interference from emotional stimuli, regardless of positive or negative valence, may be a marker of risk, particularly for multiple attempters. The results suggest that following negative life events, deficits in cognitive control may hinder suicidal adolescents from directing their attention away from hopelessness and other negative affective states. Interventions that provide tools to manage their emotions, such as distraction or mindfulness, may be especially useful in preventing suicide.

Stewart J, Glenn C, Esposito E, Cha C, et al: Cognitive control deficits differentiate adolescent suicide ideators from attempters. Journal of Clinical Psychiatry 2016; doi 10.4088/JCP.16m10647. From Harvard Medical School, Cambridge, MA; and other institutions. Funded by the NIMH; and other sources. The authors declared no competing interests.

*CSee Reference Guide.

Circadian Rhythm Disturbance and Psychosis

In a longitudinal study of adolescents and young adults at high risk of psychosis, circadian rhythm disturbances were predictive of worsening symptoms.

Background: The sleep-wake cycle is comprised of 2 interacting processes: homeostatic sleep and the circadian pacemaker. Previous research suggests disrupted sleep-wake cycles increase the severity of psychosis and predict relapse of psychotic episodes, but less is known about the effects of circadian disruptions.

Methods: Study participants, aged 12–21 years, were enrolled in an ongoing study of clinical high-risk (CHR) youth who had either attenuated positive psychosis symptoms of moderate severity or global functioning declines plus a family history of psychosis or schizotypal personality disorder. In the 34 CHR subjects and 32 healthy controls, symptoms were assessed at study entry with the Structured Interview for Prodromal Symptoms, the Structured Clinical Interview for DSM-IV, and the Global Assessment of Functioning. Circadian rhythms were measured at baseline using a wrist actigraph worn continuously for 5 days. Clinical assessments were repeated 1 year after baseline.

Results: At study entry, 3 patients in the CHR group were taking antipsychotic medication. At follow-up, 4 patients were taking antipsychotics, 2 of whom had continued to receive the medication from baseline.

At baseline, after adjusting for age, gender, and depression symptoms, CHR subjects had significantly greater rhythm fragmentation (p=0.04) and later onset of nocturnal rest (p=0.04) than controls. Baseline severity of positive symptoms was associated with greater
rhythm fragmentation, lower diurnal activity, and increased intra-daily variability in rest–activity fragmentation (all $p<0.05$). Baseline negative symptoms were significantly correlated with decreased activity during the most and least active periods of the day ($p<0.05$).

Multiple measures of circadian variability at baseline were associated with longitudinal worsening of symptoms and function among CHR adolescents. After adjustment for baseline symptoms, age, gender, and depression, severity of positive symptoms at 1 year was associated with reduced diurnal activity, reduced difference between day and night activity, reduced inter-daily stability (synchronization of circadian rhythm with light-dark cycle), and increased intra-daily variability (all $p<0.05$). Decreased diurnal activity was associated with worsening of negative symptoms ($p<0.05$). Worsening of psychosocial functioning at 1 year was predicted by reduced diurnal activity, reduced relative day/night amplitude, increased rhythm fragmentation, greater intra-daily variability, and later onset of the most active period of the day.

Discussion: The present study indicates circadian rhythm disturbance may be an important modifiable factor in the conversion to psychosis in high-risk youth. Interventions that can alter daily rhythm synchronizers include increasing the regularity of social routines such as bedtime, wake time, and meals; improving light-dark synchronization by increasing daytime light exposure and reducing nighttime exposure to light and electronic devices; and increasing daytime physical activity.

Lunsford-Avery J, Goncalves B, Brietzke E, Bressan R, et al: Adolescents at clinical-high risk for psychosis: circadian rhythm disturbances predict worsened prognosis at 1-year follow-up. Schizophrenia Research 2017; doi 10.1016/j.schres.2017.01.051. From Duke University Medical Center, Durham, NC; and other institutions. Funded by the NIH. One study author disclosed a financial relationship with a commercial source; the remaining 6 authors declared no competing interests.

### Citalopram and Emotional Regulation

In children and adolescents with anxiety disorders, treatment with citalopram (Celexa) was associated with improvement in reappraisal ability—the ability to change an emotional response by reinterpreting the meaning of the emotional stimulus—a key mechanism of emotional regulation.

Methods: Participants in this open-label observational study were 50 children and adolescents, aged 10–17 years, seeking treatment at an anxiety disorder clinic within a tertiary pediatric medical center. A total of 35 patients immediately began treatment with citalopram, and the remaining 15 had refused the medication and were placed on the clinic’s waiting list for cognitive behavioral therapy. Two computerized tests of emotional reactivity and regulation were developed for the study. The Reactivity and Regulation-Situations (REAR-S) test exposes the child to ambiguous situations taken from daily life and asks the child to rate their initial emotional reaction, reappraise the situation, and then rate the efficacy of the reappraisal. The REAR-S tests 2 aspects of negative emotional reactivity—frequency and intensity—and 3 aspects of reappraisal—uninstructed, cued, and self-efficacy. The Reactivity and Regulation-Images (REAR-I) test is similar but exposes the participant to images with threatening content. This test assesses the intensity of negative emotional reactivity, cued reappraisal ability, and reappraisal efficacy. Patients completed the computerized tasks and questionnaire-based symptom assessments at enrollment and after 8 weeks.

Results: Compared with the wait-list group, patients who received citalopram showed larger improvements in illness severity and parent ratings of anxiety after 8 weeks. Remission—a Clinical Global Impression–Severity* score of ≤2—was documented after 8 weeks in 16 patients who received citalopram and in 2 wait-listed patients (44% vs 13%, respectively; $p=0.02$).
Emotional reactivity scores decreased to a similar extent in both treatment groups. However, compared with the wait-list group, patients who received citalopram had greater improvement in cued reappraisal ability on the REAR-I. This group also showed improvement in reappraisal ability on the REAR-I, but not the REAR-S. None of the reappraisal parameters improved in the wait-list group, and these patients had a decrease in reappraisal efficacy after 8 weeks (p<0.05).

In medicated patients, improvement in reappraisal ability was modestly but significantly correlated with overall clinical improvement (correlation coefficient,* -0.03; p<0.04) and a decrease in anxiety (correlation coefficient, -0.038; p<0.02). In the combined group of patients, decreases in the intensity of emotional response on the REAR-S were correlated with decreases in anxiety (correlation coefficient, 0.44; p<0.001) and with overall clinical improvement (correlation coefficient, 0.27; p<0.05).

**Discussion:** The primary finding of this study, although preliminary, was a greater increase in cued reappraisal ability in patients taking medication, which suggests SSRI therapy may improve patients' ability to provide alternative explanations of threatening events. Medication-associated changes in reappraisal were more sensitive on the REAR-I task than the REAR-S task. This could potentially be explained by the difference in visual (REAR-I) and situational (REAR-S) tasks, which activate differing neural pathways. Clinically, the results suggest a distinction between negative emotional hyperreactivity, which is less directly controllable, and emotional regulation, which can be controlled and potentially taught.

Carthy T, Benaroya-Milshtein N, Valevski A, Apter A: Emotional reactivity and regulation following citalopram therapy in children and adolescents with anxiety disorders. *Journal of Child and Adolescent Psychopharmacology* 2017;27 (February):43–51. From Schneider Children's Medical Center of Israel, Petah Tikwa; and other institutions. Source of funding not stated. The authors declared no competing interests.

*See Reference Guide.

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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.

**Correlation Coefficient (r):** A measure of the closeness of the relationship between 2 variables. The value of r can range from -1 to 1. An r value near 1 indicated a strong positive relationship. An r-value close to zero indicates no relationship, and a negative r-value indicates a negative relationship.

**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.

**Network Meta-Analysis:** A statistical method that can provide estimates of efficacy for multiple treatment regimens, even when direct comparisons are unavailable. This method extends the traditional meta-analytic technique to allow simultaneous comparisons of the effects of multiple treatments in 2 or more studies that have 1 treatment in common. For example, if in a clinical trial comparing treatment A with treatment B, option A is determined to be superior, and a separate trial in similar patients found option B superior to a third agent, option C, a network meta-analysis of these 2 trials would allow a researcher to conclude that treatment option A is more effective than option C, even though the 2 options have never been directly compared.

**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.

**Relative Risk:** The risk of an event (or of developing a disease) relative to exposure. Relative risk is a ratio of the probability of the event occurring in the exposed group versus the control (non-exposed) 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.