CHILD & ADOLESCENT PSYCHIATRY ALERTS

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Blended CBT for Adolescent Depression

In a randomized trial, a blended intervention combining internet cognitive-behavioral therapy (ICBT) with online chat sessions with a therapist improved depression symptoms in a group of adolescents.

Methods: Study subjects were recruited using social media posts by study staff, as well as from schools and clinics in Sweden. Eligibility criteria were assessed in a telephone interview. Adolescents, aged 15–19 years, were required to meet DSM-5 criteria for a major depressive episode or to have ≥4 symptoms, including 1 core symptom, as assessed with the Beck Depression Inventory-II (BDI-II). Treatment consisted of 8 web-based CBT modules and 8 scheduled weekly 45-minute chat sessions with a therapist to review each session's material, identify problems, assist with homework, and answer questions. Controls were assigned to a therapist for weekly assessments but no treatment; they were permitted to seek outside care, which is free of charge in Sweden, and were offered the blended intervention after the study was completed. Therapists each treated 5 or 6 participants and monitored the same number of controls. The primary study outcome was change from baseline in BDI-II score.

Results: A total of 70 adolescents (mean age, 17.5 years; 67 females) were enrolled. Each week, an average of 93% of enrolled subjects completed their treatment or control assessment, and 83% of patients completed ≥50% of the active treatment weeks. Therapists spent an average of 56 minutes per week with each patient receiving blended treatment.

The blended treatment was significantly superior to the control condition at reducing depression. Among actively-treated patients, BDI-II scores decreased from a baseline mean of 32 to 16, compared with a decrease from 29 to 25 in the control group (effect size,* 0.86; $p<0.001$). Improvement in the actively-treated group persisted at the 12-week post-completion follow-up. Sixteen treated patients (46%) and 4 controls (11%) met prespecified criteria for clinically meaningful improvement ($p=0.001$). Of the patients who met DSM-5 criteria for a major depressive episode at baseline, 15 of 27 in the ICBT group and 7 of 26 controls no longer met these criteria after the 8 study weeks (56% vs 27%; $p=0.03$). Analysis of secondary outcomes showed between-treatment differences in additional measures of depression and

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in quality of life, but not in anxiety, social anxiety, or self-efficacy. There was 1 negative outcome, a patient who deteriorated during treatment and was directed to standard care, while remaining in the study.

Discussion: Unlike most other web-based CBT programs, which are either self-administered or provided with minimal therapist support, blended programs offer substantial support, either in person or electronically. Real-time texting is consistent with adolescents' media use preferences. Remission rates in this study were low compared with reported rates for in-person CBT, consistent with the high initial depression scores in this study population. However, because the vast majority of participants were female, the results may not generalize to adolescent males.

Study Rating*—15 (88%): This study met most criteria for a randomized controlled trial. However, because of the nature of the intervention, treatment was open-label, and evaluations were not completed by blinded raters.

Topooco N, Byléhn S, Nysätter E, et al: Evaluating the efficacy of internet-delivered cognitive behavioral therapy blended with synchronous chat sessions to treat adolescent depression: randomized controlled trial. *Journal of Medical Internet Research* 2019; doi 10.2196/13393. From Linköping University, Sweden; and other institutions. **Funded by the Swedish Central Bank; and other sources. The authors declared no competing interests.**

***See Reference Guide.**

Family-Focused Therapy in High Risk Youth

In a randomized trial, family-focused therapy (FFT) delayed the onset of mood episodes in high-risk children and adolescents with early or subthreshold symptoms. However, treatment did not reduce time to recovery from existing symptoms or lower rates of conversion to syndromal bipolar disorder.

Methods: The study enrolled 127 patients, aged 9–17 years (mean age, 13 years), who met DSM criteria for unspecified bipolar disorder or major depressive disorder, had a near relative with a lifetime history of bipolar disorder, and had at least moderate current mood symptoms. Randomized treatment with either FFT or a psychoeducational control was conducted at 3 clinical centers. FFT consisted of 12 hour-long child-and-parent sessions offered over 4 months and included psychoeducation, communication and enhancement training, and problem-solving skills training. The control psychoeducational treatment was conducted in mixed youth-only or family sessions that occupied the same amount of time as FFT. Patients could receive medication if requested or clinically indicated, in which case prescribers followed a study-specific algorithm. Outcomes were assessed with the Adolescent Longitudinal Interval Follow-up Evaluation and associated Psychiatric Status Ratings. The study had 2 primary outcomes: time from treatment assignment to the beginning of a recovery period, and for those who recovered, time to a new mood episode.

Results: Of the 127 patients enrolled, 90 met the mood recovery criteria at some point during follow-up. The median time to recovery was 23–24 weeks, with no difference between treatment groups. During follow-up, 71 patients (79% of those who recovered) experienced a new mood episode: 70 major depressive and 12 manic. The frequency of new mood episodes did not differ between the treatment groups. However, patients who received FFT had a longer time to a new episode than controls (hazard ratio,* 0.55; p=0.02). The median time from randomization to a new mood episode was 81 weeks with FFT and 63 weeks with control treatment. The number of patients who converted to bipolar disorder was similar in the 2 groups, with 9 converting to manic or mixed episodes and 9 experiencing hypomanic episodes.

Discussion: Both groups showed significant improvement in mood symptoms during the treatment period, followed by a leveling of symptoms. The finding that FFT delayed the onset of new

mood disorder episodes is encouraging. However, changes in family function were not evaluated and their relationship to symptom course warrants investigation.

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

Miklowitz D, Schneck C, Walshaw P: Effects of family-focused therapy vs enhanced usual care for symptomatic youths at high risk for bipolar disorder: a randomized clinical trial. *JAMA Psychiatry* 2020; doi 10.1001/jamapsychiatry.2019.4520. From the David Geffen School of Medicine, University of California, Los Angeles; and other institutions. **Funded by the NIMH; and other sources. Eight of 9 study authors disclosed potentially relevant financial relationships; the remaining author declared no competing interests.**

***See Reference Guide.**

Esketamine for Pediatric Depression

In March 2019, intranasal esketamine (*Spravato*) received FDA approval to treat resistant depression in adults. The agent acts rapidly, and a brief course of treatment has been shown to produce long-lasting benefits. Clinical trials to test the efficacy of esketamine in adolescents have already begun. However, research has suggested that repeated exposure to ketamine-like drugs during development can permanently disrupt neurodevelopment and have detrimental effects on long-term cognitive and behavioral outcomes.

Ketamine is believed to act on depression by preferentially blocking N-methyl-D-aspartate (NMDA) receptors on inhibitory interneurons, including those expressing parvalbumin, which are not fully functional in adolescents. In animal models, repeated exposure to NMDA receptor antagonists impairs maturation of parvalbumin neurons, and reduces the number of these neurons in the medial prefrontal cortex, which can lead to disorganized prefrontal cortex output in adulthood.

Some preclinical data suggest that higher or more frequent ketamine doses may be needed to achieve antidepressant effects in adolescents than in adults, possibly because the immaturity of parvalbumin interneurons blunts the therapeutic effect. This may be concerning given that at doses typically used for treatment-resistant depression in adults, ketamine has been reported to induce schizophrenia-like dissociative symptoms. Although exposure to modest esketamine dosing for sedation or analgesia during adolescence might not carry a risk of lasting damage, FDA guidelines for esketamine maintenance of treatment-resistant depression in adults recommend continued weekly or biweekly administration. Despite clinical eagerness for an antidepressant that produces rapid improvement, the authors suggest that extensive screening for schizophrenia risk factors may be prudent before referring potential candidates to adolescent esketamine clinical trials.

Zimmerman K, Richardson R, Baker K: Esketamine as a treatment for pediatric depression: questions of safety and efficacy. *Lancet Psychiatry* 2020; doi 10.1016/S2215-0366(19)30521-8. From the University of New South Wales, Australia. **Funded by the Australian Research Council. The authors declared no competing interests.**

Metabolic Syndrome in Children

Despite a lack of consensus on the definition of metabolic syndrome in children and adolescents, there is general agreement that preventing and treating obesity should be the first-line approach in order to reduce cardiovascular risk due to the syndrome.

In ways that are not fully understood, metabolic syndrome is at least partly the result of an interaction between obesity, insulin resistance, and a pro-inflammatory state. Besides obesity, the other components of the syndrome are hypertension, dyslipidemia, impaired glucose metabolism and type 2 diabetes, and non-alcoholic fatty liver disease. Interventions that address 1 element of the disorder, such as dietary changes and increased physical activity, could be useful in ameliorating others via a common mechanism of weight loss.

Evidence suggests these types of behavioral interventions have larger effects in children than in adolescents, emphasizing the importance of early intervention.

Guidelines from the American Academy of Pediatrics describe the appropriate modifications in diet and nutrition. The primary goal of intervention should be reducing caloric intake, but other measures, such as reducing sugar and increasing fiber intake, may improve glucose abnormalities. Physical activity should be encouraged in preschool children, and those aged 6–17 years should engage in moderate to vigorous physical activity for ≥60 minutes each day. Healthy sleep habits and limiting screen time should be addressed. Pharmacotherapy of obesity in pediatric patients is poorly studied. Orlistat is the only FDA-approved agent for pediatric weight reduction, and only in adolescents aged >12 years. After ruling out substance abuse and eating disorders, bariatric surgery may be considered for patients with extreme obesity who have completed their growth and pubertal development.

The other components of metabolic syndrome are likely to improve with weight loss and lifestyle modifications, but may also require specific treatment. Hypertension should be addressed with lifestyle modification, followed by medication if necessary. The current target blood pressure in adolescents is <130/80 mmHg. Angiotensin-converting enzyme inhibitors, angiotensin receptor blockers, calcium channel blockers, and thiazide diuretics are all similarly effective in children. Dyslipidemia in children with metabolic syndrome usually consists of elevated triglycerides and low HDL cholesterol. Fish oil supplements may be considered. Glucose impairment seldom requires medication, but type 2 diabetes calls for treatment with metformin, followed by insulin. Probiotics and omega-3 fatty acids may ameliorate liver disease.

Fornari E, Maffeis C: Treatment of metabolic syndrome in children. *Frontiers in Endocrinology* 2019; doi 10.3389/endo.2019.00702. From the University of Verona, Italy. **Funded by the University of Verona. The authors declared no competing interests.**

Common Drug Trade Names: metformin—Glucophage; orlistat—Xenical

Hospitalization and Repeat Self-Injury Risk

According to the results of a retrospective study of service use patterns in adolescents who engaged in self-injury, patients admitted to a psychiatric facility within 7 days of the index self-injury were twice as likely as those who were not hospitalized to have another episode of self-injury in the subsequent year.

Methods: Data for >31,000 youths who were medically treated for self-injury between 2007 and 2016 were collected from a commercial insurance claims database. For inclusion in the cohort, patients were required to be aged 6–18 years and to have had continuous insurance coverage for ≥1 year before and after the index self-injury. Patterns of service use in the year before and after the index self-injury episode were compared between patients who were and were not hospitalized following the initial self-injury. Inpatient admissions to any type of facility (e.g., psychiatric facilities, residential substance abuse facilities, comprehensive inpatient rehabilitation facilities), outpatient psychiatric visits, emergency department visits, and medication use were assessed. The main outcome of interest was subsequent medically treated self-injury in the year following the index episode.

Results: Of the 31,147 patients with a self-injurious episode, 2027 (6.5%) were admitted to a psychiatric facility within 1 week. In the year before the index self-injury, few youths were engaged in outpatient psychiatric care: 12% of the hospitalized group, compared with 2% of those who were not admitted ($p<0.001$). Despite significantly higher rates of participation in outpatient psychiatric care after the index self-injury episode (25% vs 3%; $p<0.001$) and medication use (82% vs 65%; $p<0.001$), the rate of subsequent self-injury was significantly higher among patients who were admitted for the initial episode (5.4% vs 1.4; hazard ratio,* 2.1; $p<0.001$).

Discussion: While inpatient care may have led to higher rates of subsequent engagement in outpatient care, patients attended far fewer sessions, on average 7–8 in the subsequent year, than would be recommended with a suicide-specific intervention. Because the study data do not include information on disease severity, symptom changes, or treatment response, it is possible that the observed between-group differences are driven by illness severity, rather than a direct effect of inpatient care upon future risk. Regardless, hospitalization following self-injury appears to be a strong indicator of increased risk for subsequent self-injury episodes.

Adrian M, DeCou C, Gold L: Medically-treated self-injury among children and adolescents: repeated attempts and service use over 1 year. *Psychiatric Services* 2019; doi 10.1176/appi.ps.201900152. From the University of Washington, Seattle; and Harborview Injury Prevention and Research Center, Seattle. **Funded by the National Institute of Child Health and Development; and other sources. The authors declared no competing interests.**

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School-Based Intervention for Anxiety

A randomized trial confirmed the efficacy of school-based cognitive-behavioral interventions in reducing anxiety symptoms in adolescents. The study did not demonstrate noninferiority of a brief intervention to standard CBT.

Methods: The CBT programs were delivered in 15 junior high schools in Norway. Adolescents, aged 12–16 years, were invited to participate if they had self- or parent-reported anxiety symptoms above a threshold on the Spence Children's Anxiety Scale (SCAS), with some interference in daily life. The 313 participants were initially randomized to the Cool Kids CBT program, a brief CBT intervention (Vaag) developed by the investigators, or a wait-list control condition. After 10 weeks, adolescents on the waiting list were rerandomized to receive Cool Kids or Vaag. In contrast to the Cool Kids program, which incorporates 10 weekly sessions, Vaag is a 5-session group program, also delivered over 10 weeks, but with 4 weekly sessions, a 5-week period of mostly unassisted exposure tasks, and a final joint youth-parent session. Both programs were delivered in school during regular classroom hours. Primary study outcomes were changes in youth and parent ratings of anxiety symptoms on the youth and parent SCAS and changes in impairment, assessed with the Child Anxiety Life Interference Scale.

Results: At baseline, participants' scores for anxiety and impairment were either in the clinical range or slightly below. Compared with the wait-list controls, participants in the combined CBT programs had significantly larger decreases in SCAS scores, with effect sizes* of 0.34 ($p=0.001$) and 0.53 ($p<0.001$) for self and parent ratings, respectively. Parent ratings of impairment also showed greater improvement with CBT than with the wait list control (effect size, 0.51; $p<0.001$). Although patients in both CBT groups improved, the between-group difference in self-reported SCAS scores (7.1 point for Vaag and 10.5 for Cool Kids) did not meet the study's prespecified criteria for noninferiority, leading the authors to conclude that brief CBT cannot replace standard CBT. Improvements with both interventions were sustained at 1-year follow-up.

Discussion: Previous studies and meta-analyses of school-based CBT interventions for anxiety have shown small-to-moderate effects. Many of these studies have lacked methodological rigor, and most evaluated CBT interventions consisting of ≥8 sessions. Because brief CBT has potential advantages in the school setting (i.e., it is less costly and easier to implement), additional research appears to be warranted.

Mowatt Haugland B, Haaland A, Baste V, et al: Effectiveness of brief and standard school-based cognitive-behavioral interventions for adolescents with anxiety: a randomized non-inferiority study. *Journal of the American Academy of Child and Adolescent Psychiatry* 2020; doi 10.1016/j.jaac.2019.12.003. From the Norwegian Research Center, Norway; and other institutions. **Funded by the Research Council of Norway; and other sources. One of 11 study authors disclosed a relevant financial relationship; the remaining authors declared no competing interests.**

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Oral Contraceptives and Depression

Research has suggested a link between oral contraceptives (OCs) and increased risk of developing depression in adolescents. A longitudinal study found higher rates of several depressive symptoms in 16-year old girls using OCs than in those who were not. However, symptom levels were not elevated in the same girls later in adolescence or in young adulthood.

Methods: Data were collected from a Danish national study, in which participants of both sexes were interviewed at an average age of 11 years, with follow-up waves conducted at ages of 13, 16, 19, 22, and 25 years. The present analysis was limited to girls who participated in ≥1 interview between the ages of 16 and 25 years. Oral contraceptive use was self-reported. Depression symptoms before age 16 years were measured using the Youth Self-Report, a version of the Child Behavior Checklist, which assesses crying, eating, sleeping, suicidal ideation, self-harm, feelings of worthlessness and guilt, energy, activity, sadness, and anhedonia. At older ages, symptoms were assessed using the adult version of this instrument, the Adult Self-Report.

Results: A total of 1010 young women were interviewed at least once, with an average of 3 assessments per participant. For the cohort overall, oral contraceptive use was not associated with concurrent depressive symptoms. However, the 63% of girls using OCs at age 16 years reported significantly more crying (odds ratio [OR],* 1.89; p<0.001), eating problems (OR, 1.54; p=0.009), and hypersomnia (OR, 1.68; p=0.006) than non-users. Adjustment for previous use of OCs and for previous depressive symptoms weakened the association somewhat. The core symptoms of depression—anhedonia and sadness—were unaffected by OC use, but these are less typical of adolescent depression than non-core physical symptoms. Longer OC use, up to 12 years, was associated with decreased depression symptom scores, although not significantly.

Discussion: The weakened association when the analysis was adjusted for previous OC use may suggest that depression increases the likelihood of starting OC use, rather than the reverse. Additionally, OC use to treat cycle-related mood problems may have influenced the results. While these results do not support limiting the use of OCs in adolescent girls to counter the potential increase in depressive symptoms, monitoring treated girls is recommended.

De Wit A, Booij S, Giltay E, et al: Association of use of oral contraceptives with depressive symptoms among adolescents and young women. *JAMA Psychiatry* 2020;77 (January):52–59. From the University of Groningen, the Netherlands; and other institutions. **Funded by the Netherlands Organization for Scientific Research; and other sources. Three of 6 study authors disclosed potentially relevant financial relationships; the remaining authors declared no competing interests.**

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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.

Hazard Ratio: A measure of the risk of an event relative to exposure, or the probability of an event occurring in an exposed group versus a non-exposed group. A hazard ratio of 0.5 indicates that 1 group has half the risk of the other 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). Checklists are posted at alertpubs.com.

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