

# CHILD & ADOLESCENT PSYCHIATRY ALERTS

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**Important Reminder . . . Delivery of *Child & Adolescent Psychiatry Alerts* is now 100% electronic.**

## Evening Methylphenidate

A new extended-release methylphenidate formulation (*Jornay PM*, formerly HLD200), designed to be administered in the evening in order to control early morning ADHD symptoms, has received FDA approval for use in patients aged  $\geq 6$  years. The proprietary delivery system of *Jornay PM* delays initial methylphenidate release for up to 10 hours, followed by a controlled-release throughout the day. Administration timing can be adjusted between 6:30 and 9:30 PM to optimize early-morning and later-day symptom control. In clinical trials, adverse effects of *Jornay PM* were generally those expected with methylphenidate including appetite suppression, weight loss, insomnia, dizziness, and increased blood pressure. Additional adverse reactions specific to *Jornay PM* included headache, psychomotor hyperactivity, and mood swings. Commercial availability of *Jornay PM* is expected in the early half of 2019.

Ironshore Pharmaceuticals announces FDA approval of *Jornay PM* (methylphenidate) extended-release capsules CII for the treatment of ADHD [press release]. George Town, Cayman Islands; Ironshore Pharmaceuticals: August 9, 2018. Available at <http://www.ironshorepharma.com/pdf/Ironshore-Announces-FDA-Approval-JORNAY-PM.pdf>.

## Bridging Intervention for Adolescent Suicidality After Discharge

Risk for suicidal behavior after hospital discharge is exceptionally high, and there are currently no interventions specifically designed to decrease the risk of suicide attempt during the transition from inpatient to outpatient care. In a preliminary study, a brief inpatient intervention, paired with a post-discharge smartphone app, showed promise in reducing suicide attempts in adolescents hospitalized for suicidality.

**Background:** The NIMH-funded intervention, As Safe as Possible (ASAP), consists of 4 modules that are completed in the hospital with the aid of a therapist. The intervention includes motivational interviewing, psychoeducation, developing a safety plan, behavioral activation, affect regulation strategies, use of the app, and review of skills with the patient and family. The phone app, BRITE, is meant to be used after discharge. Patients receive daily text messages to rate their level of emotional distress and receive tailored information on distress tolerance and emotional regulation strategies, the personalized safety plan, and clinical contact

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options if needed. The program also includes post-discharge bridging telephone contact with the ASAP therapist, who aids with the transition to a community provider.

**Methods:** A pilot study of the ASAP intervention was conducted in patients, aged 12–18 years, hospitalized with recent suicidal ideation with a plan or intent or a recent suicide attempt. Patients were randomly assigned to receive ASAP plus treatment as usual or only treatment as usual and were followed for 24 weeks. The primary study outcome was time to suicide attempt.

**Results:** A total of 66 adolescents participated in the study. They had a mean age of 15 years, 89% were girls, and 77% were white. Most (86%) had a clinical diagnosis of major depression, and 58% had an anxiety disorder. Patients took a mean of 2.7 hours to complete the ASAP inpatient intervention, over a median of 3 sessions. Of the 34 patients who received ASAP, 10 had a session with their families, and 26 had  $\geq 1$  bridging telephone call with their therapist.

ASAP was numerically but not statistically superior to treatment as usual at reducing suicide attempts (5 vs 9 attempts, 16% vs 31%) and at prolonging the time to the next attempt (hazard ratio,\* 0.49). ASAP had a stronger, but still nonsignificant, effect in patients with a prior suicide attempt (hazard ratio, 0.23). After adjusting for age, the effect was significant (hazard ratio, 0.19;  $p=0.03$ ). ASAP was not associated with a larger decrease in suicidal ideation than treatment as usual, but patients who received ASAP showed a larger increase in social support.

Most patients in the ASAP group used the smartphone app at least once. They rated their mood a median of 19 times, three-fourths received content about their concerns, and nearly half activated their contacts as part of their safety plan. Frequency of app use was not associated with decreased suicidal ideation or risk of suicide attempt.

Participants gave high ratings for treatment satisfaction whether they received ASAP or only treatment as usual. Adolescents who received ASAP were less likely than controls to participate in outpatient therapy but had otherwise similar levels of service use post-discharge.

**Discussion:** ASAP was developed to address a critical gap in clinical care between hospital discharge and outpatient care, when risk of a suicide attempt is high. The results of the present study indicate promise, although a larger sample size would be required to show statistical significance.

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

Kennard B, Goldstein T, Foxwell A, McMakin D, et al: As Safe as Possible (ASAP): a brief app-supported inpatient intervention to prevent postdischarge suicidal behavior in hospitalized, suicidal adolescents. *American Journal of Psychiatry* 2018; doi 10.1176/appi.ajp.2018.17101151. From the University of Texas Southwestern Medical Center, Dallas; and other institutions. **Funded by the NIMH. Five of 15 study authors disclosed potentially relevant financial relationships; the remaining authors declared no competing interests.**

\*See Reference Guide.

## Suicide Prevention: Unintended Consequences

According to a literature review, suicide prevention programs can have unintended negative consequences. While these adverse effects are uncommon and do not outweigh the benefits of the programs, they are rarely evaluated, and a more systematic approach to identifying, reporting, and preventing them is needed.

A literature search identified peer-reviewed publications addressing unanticipated consequences of suicide prevention programs, including program evaluations, ecological studies, randomized controlled trials, cohort studies, and case-control studies. Because of the scarcity of articles focusing on youth programs, literature on programs that targeted a broader age range were also included. The review encompassed a total of 22 articles published since 1989, including 17 studies that directly assessed adverse effects.

**Community-based outreach and awareness programs** have been associated with an increase in maladaptive attitudes related to suicide or help-seeking in some young people. A small minority found the information upsetting. These reports are limited to the early years of the review, when representations of suicide were more graphic than they are now. A more recent article showed young people with depression or experiencing suicidality to be less likely to report help-seeking attitudes after being exposed to a media campaign.

**Early identification screening programs** have been assessed in several studies, with mixed results. In 1 study, a minority of students found it distressing to answer questions about suicidal thoughts and self-harm. Several other studies found no evidence of an iatrogenic effect of screening. In another study, students at increased risk for suicide reported less distress after answering screening questions, compared with unexposed high-risk students.

**Skills training programs**, which enhance problem-solving, coping, social, and other skills, have been evaluated in 2 studies that found adverse effects on participants' behavior, possibly due to a contagion effect of clustering high-risk students together.

**Crisis hotline** adverse effects have not been studied in young people. However, studies in adults suggest potential adverse consequences due to the resulting referrals (e.g., high costs, long waits for help, referral for inappropriate services). Although not identified in the studies in the literature review, there is also the potential for adverse consequences when there are insufficient resources to help young people identified as at risk.

Kuiper N, Goldston D, Garraza L, Walrath C, et al: Examining the unanticipated adverse consequences of youth suicide prevention strategies: a literature review with recommendations for prevention programs. *Suicide and Life-Threatening Behavior* 2018; doi 10.1111/sltb.12492. From ICF, Atlanta, GA; Duke University, Durham, NC; and other institutions. **Funded by the Substance Abuse and Mental Health Services Administration. The authors did not include disclosure of potential conflicts of interest.**

## Internet CBT for OCD in Children

In a pilot study, an internet-delivered cognitive behavioral therapy for obsessive-compulsive disorder was feasible and acceptable and had beneficial effects in younger children, while using about one-third the amount of therapist time as face-to-face CBT.

**Background:** The initial internet CBT program, called BIP OCD was developed by the study authors and evaluated in adolescents. BIP OCD Junior was adapted for use in younger children, mainly by expanding the role of parents. The program uses computer-delivered text, films, illustrations, and exercises focusing on psychoeducation, exposure with response prevention, and relapse prevention. Parents and children, each with a separate login account, work through 12 chapters with tailored content. Throughout the program, a clinical psychologist responds to email queries from family members, usually within 24 hours on weekdays.

**Methods:** Participants in this study were 11 children (mean age, 9.5 years; 7 girls) who met DSM-5 criteria for OCD and had a baseline Children's Yale-Brown Obsessive Compulsive Scale (CY-BOCS) score of  $\geq 16$ . Stable concomitant medication was permitted. The primary study outcome was change from baseline in the CY-BOCS score, with response defined as a  $\geq 35\%$  decrease plus a Clinical Global Impression-Improvement (CGI-I)\* score of  $\leq 2$ , and remission defined as a score of  $\leq 12$  plus a CGI-I score  $\leq 2$ .

**Results:** All participants completed treatment and a 3-month post-treatment follow-up. The children had a significant mean decrease in the CY-BOCS score from 21 pretreatment to 10 post-treatment ( $p < 0.001$ ; effect size, \* 1.86). Modest additional decreases were seen at the 3-month follow-up (mean score, 8; effect size, 0.30). Child- and parent-rated OCD symptom severity also improved during treatment. At post-treatment, 8 children (73%) were classified as

responders, including 5 (46%) who met remission criteria. At the 3-month follow-up, 7 children (64%) had achieved remission. Families completed an average of 11 of the 12 chapters. Clinicians had a mean input of 22 minutes per week per participant. Parents and children rated the treatment highly and said they would recommend it to others.

**Discussion:** Effect sizes in this study were similar to those previously shown in adolescents who participated in BIP OCD and to face-to-face CBT for OCD in children. While the results are positive, the study sample was small, and larger randomized trials are needed.

Aspvall K, Andrén P, Lenhard F, Andersson E, et al: Internet-delivered cognitive behavioural therapy for young children with obsessive-compulsive disorder: development and initial evaluation of the BIP OCD Junior programme. *BJPsych Open* 2018;4:106–112. doi 10.1192/bjo.2018.10. From Karolinska Institutet, Stockholm, Sweden; and other institutions. **Funded by the Swedish Research Council for Health, Working Life and Welfare. This research group developed the iCBT program investigated in the study, but disclosure of additional potential competing interests was not included.**

\*See Reference Guide.

## Cardiovascular Safety of Atypical Antipsychotics

In a large cohort study, initiation of atypical antipsychotic medications was associated with an increased rate of serious cardiovascular events in Medicaid-insured young people. Risk was intensified with increasing antipsychotic doses and with concomitant use of SSRI or SNRI antidepressants.

**Methods:** The analysis was based on statewide Medicaid claims data from California, Florida, Illinois, and New Jersey. The study cohort consisted of 74,700 patients, aged 5–20 years, who began treatment with an oral atypical antipsychotic between 2005 and 2009. During each month of follow-up, atypical antipsychotic use was categorized as current or former, and rates of cardiovascular events were compared for periods of use and non-use. The primary study outcome was a cardiovascular event (i.e., acute myocardial infarction, stroke, ventricular arrhythmia, aortic or thoracic aneurysm, heart failure, and other cardiovascular events) resulting in inpatient hospitalization or an emergency-department visit.

**Results:** Most of the study cohort were between the ages of 5 and 14 years (68%) and male (63%); more than half were receiving other psychotropic medications—usually stimulants or antidepressants—before atypical antipsychotics were prescribed. Patients received atypicals for an average of about 10 months and were followed for a mean of 2 years.

A total of 142 cardiovascular events occurred during follow-up. Current atypical antipsychotic use was associated with an increased risk of these events, relative to former use (relative risk [RR],\* 1.55). Higher doses conferred greater risk, with an RR of 2.04 in those receiving >3.75 mg/day risperidone (*Risperdal*) equivalents, compared with ≤1.25 mg/day. Duration of exposure was not related to cardiovascular risk. However, during atypical antipsychotic exposure, concomitant SSRI/SNRI use was associated with increased cardiovascular risk (RR, 1.61) compared with non-use. Stimulant use did not affect risk of a cardiovascular event.

**Discussion:** Second-generation antipsychotic-related risk of serious cardiovascular events has been observed in population-based studies, mostly in adults. Although the incidence of cardiovascular events in this population was low, atypical antipsychotics have been associated with hyperlipidemia, hyperglycemia, type 2 diabetes, prolactin disturbances, and weight gain, all of which are a greater risk for children. Future research should address the comparative risk of different atypical antipsychotics in young patients.

Burcu M, Zito J, Safer D, Magder L, et al: Cardiovascular events following treatment initiation with atypical antipsychotic medications in publicly insured U.S. youth. *Journal of Child and Adolescent Psychopharmacology* 2018; doi 10.1089/cap.2017.0121. From the University of Maryland and Johns Hopkins Medical Institutions, Baltimore, MD. **Funded by the FDA; and the University of Maryland. The authors declared no competing interests.**

\*See Reference Guide.

## Omega-3s for Adolescent Depression

Monotherapy with omega-3 fatty acids was not superior to placebo in a randomized trial in adolescents with depression. This finding is consistent with several large trials in adults but contrasts with the few prior studies in pediatric depression.

**Methods:** Study participants were unmedicated patients, aged 12–19 years, with a primary diagnosis of major depressive disorder and a current episode duration of  $\geq 6$  weeks. Stimulants were the only permitted background psychotropic medication, and psychotherapy could not be initiated or altered during the 10-week study. Active treatment consisted of omega-3 fatty acids with a 2:1 ratio of eicosapentaenoic acid (EPA) to docosahexaenoic acid (DHA), titrated to a maximum combined dosage of 3.6 g/day. The primary study outcome was treatment response, defined as a  $\geq 50\%$  improvement from baseline on the Children's Depression Rating Scale-Revised (CDRS-R), correcting for the 17-item base score, or reaching a score of  $\leq 28$ .

**Results:** The trial enrolled 48 adolescents (42% boys; mean age, 16 years; mean baseline CDRS-R score, 50). The mean final omega-3 dosage was 3.4 g/day in the study completers: 18 of 21 patients in the omega-3 group and 21 of 27 in the placebo group. The rate of response was 43% in the omega-3 group and 50% in the placebo group, a nonsignificant difference. The 2 groups did not differ in any secondary treatment outcomes, including symptoms that were of special interest: anhedonia, irritability, or suicidality. Fatty acids had no significant adverse effects.

**Discussion:** It has been proposed that baseline inflammation may moderate clinical response to omega-3 fatty acids in depression. However, in this study, anhedonia, thought to be related to inflammation, did not improve significantly with active treatment. It is possible that omega-3 fatty acid monotherapy may be effective at higher doses, or in less severe depression.

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

Gabbay V, Freed R, Alonso C, Senger S, et al: A double-blind placebo-controlled trial of omega-3 fatty acids as a monotherapy for adolescent depression. *Journal of Clinical Psychiatry* 2018; doi 10.4088/JCP.17m11596. From the Icahn School of Medicine at Mount Sinai, New York, NY; and other institutions. **Funded by the NIH. The authors declared no competing interests.**

\*See Reference Guide.

## Therapeutic Game for Emotional Regulation

In a randomized trial, RETHink, an online therapeutic video game, reduced depressive symptoms and emotional problems in healthy children and adolescents.

**Background:** The RETHink game is based on the principles of Rational Emotive Behavioral Therapy (REBT) and Rational Emotive Behavioral Education (REBE). These evidence-based interventions focus on cultivating rational beliefs to replace irrational ones and fostering positive emotions and social behaviors. RETHink is a standalone computer game in which the player navigates 7 successive levels with such objectives as identifying cognitive processes, linking them to emotional and behavioral reactions, and learning problem-solving and relaxation skills.

**Methods:** Study participants were healthy children and adolescents, aged 10–16 years, recruited from a single middle school. They were randomly assigned to play the RETHink game, receive standard REBE in a classroom format, or be on a waiting list. The psychological content of RETHink and REBE were the same, as was the time spent: 7 modules with 50 minutes per module. Both programs were delivered in school after the end of classes and completed within 1 month. A REBE certified psychologist delivered the didactic program and assisted with the computer game. The primary study outcomes were emotional symptoms, measured with the child version of the Strengths and Difficulties Questionnaire (SDQ), and depressive symptoms, measured with the Early Adolescent Temperament Questionnaire–Revised (EATQ-R).

**Results:** Of 165 young people who volunteered for the study, 23 dropped out before the initial assessment; the remaining 142 completed the intervention and the pre-, mid-, and post-treatment assessments. The sample consisted of 91 girls and 51 boys; 72% were in grades 5–8, and 28% were in grades 9–10.

Patients in both the RETHink and REBE groups demonstrated improvements over time on measures of both emotional symptoms and depression. However, effects were stronger for RETHink, and improvements in the REBE group were not statistically significant. Wait-listed patients showed small improvements in depressive symptoms but slightly worsened emotional symptom scores. (See table.) Both the RETHink and REBE groups also showed significant improvement in secondary

outcomes, including EATQ-R scores for attention and in the control dimension of the Emotion-Regulation Index for Children and Adolescents

Primary study outcomes: Pre- to immediately post-treatment			
Outcome	Effect size;* significance vs baseline		
	REThink	REBE	Waitlist
SDQ emotional symptoms	0.46; p=0.002	0.15; p=NS	-0.13; P=NS
EATQ-R depressive mood	0.84; p<0.001	0.26; p=NS	0.12; p=NS

(ERICA). Only the RETHink group showed significant improvement in awareness on the ERICA instrument. There were marginal differences between the groups in SDQ relationship problems and no differences in SDQ prosocial behavior. Participant satisfaction with RETHink was higher than REBE mid-treatment, but the 2 were rated as equally satisfactory at the end of treatment.

**Discussion:** These findings suggest that RETHink could have a significant impact on emotional well-being and ability to regulate emotions. The high satisfaction ratings indicate that the RETHink game has the potential for wide use. However, the study was conducted in a non-clinical sample, which while it support the use of RETHink as a general prevention effort, may not generalize to patients with clinical psychopathology.

**Study Rating\*—15 (88%):** This study met most criteria for a randomized controlled trial; however, the report did not include information on blinding of symptom assessors.

David O, Cardoso R, Matu S: Is RETHink therapeutic game effective in preventing emotional disorders in children and adolescents? Outcomes of a randomized clinical trial. *European Child and Adolescent Psychiatry* 2018; doi 10.1007/s00787-018-1192-2. From Babes-Bolyai University, Romania. **Funded by the Romanian National Authority for Scientific Research. The authors declared no competing interests.**

\*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.

**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.

**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.

**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](http://www.alertpubs.com).

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