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Adding Fluoxetine to CBT for Depression

In a placebo-controlled trial in adolescents and young adults with severe depression, adding fluoxetine (*Prozac*) did not improve the overall efficacy of cognitive-behavioral therapy. However, added medication might be helpful in young adults and in those with comorbid anxiety symptoms.

Methods: Participants, aged 15–25 years, were enrolled after seeking treatment at specialized youth mental health centers. They were required to have Montgomery-Asberg Depression Rating Scale (MADRS) scores of ≥20, indicating moderate or greater severity. There were few restrictions on enrollment; participants were not excluded if they had suicidal ideation or prior suicidal behavior. All patients received weekly sessions of manualized CBT, consisting of 7 core modules: psychoeducation; understanding and monitoring emotions; behavioral activation; the ABC model and chain analysis; identifying automatic thoughts; working with unhelpful thinking; and relapse prevention. Additional modules targeted at individual's specific difficulties (e.g., distress tolerance, social anxiety, insomnia) could be added as needed. Participants also received randomly assigned double-blind fluoxetine, started at 20 mg/day and increased to 40 mg/day after 4 weeks if needed, or placebo. The primary study outcome was change in MADRS score at 12 weeks.

Results: Of 153 patients enrolled in the study, 32% were aged <18 years, 40% were experiencing their first depressive episode, and most were suffering from severe depression. A large majority (93%) had suicidal ideation, and >60% had comorbid anxiety.

Baseline MADRS scores did not differ significantly between the placebo and fluoxetine groups: 33.6 and 32.2, respectively. After 12 weeks of treatment, scores improved to 19.9 and 17.1, respectively, but there continued to be no significant difference between the groups. Remission, defined as a MADRS score ≤7, occurred in 24% of the fluoxetine group and in 19% of the placebo group, a statistically nonsignificant difference. Patients who received fluoxetine had a larger decrease in anxiety symptoms measured with the Generalized Anxiety Disorder 7-item scale (5.3 points vs 3.2 points; p=0.02). Changes in functioning and quality of life did not differ between the

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treatment groups. In a follow-up 26 weeks from the start of treatment, the groups still did not differ significantly in average MADRS scores or in rates of remission. In patients aged ≥18 years, fluoxetine produced significantly greater reductions in MADRS score than placebo (p=0.02), and rates of remission were also higher in the fluoxetine group (29% versus 15%; p=0.09).

During the 12 weeks of active treatment, there were 5 suicide attempts in the placebo group and 1 in the fluoxetine group. In contrast, 17% of the fluoxetine group and 7% of the placebo group had new-onset nonsuicidal self-injury. The groups did not differ significantly in the frequency of new-onset or worsening suicidal ideation or new suicidal acts or behavior.

Discussion: While these results do not support the addition of fluoxetine to CBT for moderate-to-severe depression in patients aged ≤18 years, they do suggest the combination may be useful in the treatment of comorbid anxiety. Importantly, rates of remission were low regardless of study treatment, emphasizing the need for more effective treatments for depression in young patients.

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

Davey C, Chanen A, Hetrick S, Cotton S, et al: The addition of fluoxetine to cognitive behavioural therapy for youth depression (YoDA-C): a randomised, double-blind, placebo-controlled, multicentre clinical trial. *Lancet Psychiatry* 2019;6 (September):735–743. doi 10.1016/S2215-0366(19)30215-9. From Orygen, the National Centre of Excellence in Youth Mental Health, Melbourne, Australia; and other institutions. **Funded by the Australian National Health and Medical Research Council. Four of 20 study authors disclosed potentially relevant financial relationships; the remaining authors declared no competing interests.**

***See Reference Guide.**

Pharmacotherapy for Substance Use Disorders

According to a literature review, pharmacotherapy may be a useful adjunct to the psychosocial therapies that are first-line treatment for substance use disorders in adolescents. There are almost no FDA-approved drug treatments for these disorders in youths. However, there is evidence some of the medications that are effective in adults might benefit adolescents, enhancing the often modest efficacy of psychosocial treatments.

Alcohol is the substance most commonly used by adolescents. Naltrexone is approved for treating both alcohol and opioid use disorders in those aged ≥18 years. The literature suggests naltrexone is safe and possibly effective in alcohol use disorder in adolescents, with a small (n=22) placebo-controlled crossover trial showing reduced alcohol consumption and reduced craving. In a larger study of 128 binge-drinking subjects who were not seeking treatment, naltrexone reduced some but not all measures of alcohol consumption. N-acetylcysteine (NAC), available over the counter and FDA-approved for other indications in pediatric populations, reduced alcohol use in a secondary analysis of data from a cannabis cessation trial in adolescents. Ondansetron was safe and well tolerated in a pilot study in treatment-seeking adolescents, but the lack of a control group did not permit conclusions about its effects on alcohol consumption.

NAC and topiramate have each been investigated in a clinical trial for cannabis use disorder. Among 118 treatment-seeking adolescents and young adults, those randomly assigned to receive NAC had twice the rate of abstinence from cannabis as the placebo group. Adding to the appeal of NAC is its safety, tolerability, low cost, and over-the-counter availability. Topiramate reduced overall cannabis consumption in a placebo-controlled study of 66 adolescents and young adults but did not improve abstinence rates, and adverse effects and drug interactions are a concern.

Rates of smoking are decreasing in adolescents, but the growth in vaping is a concern. Three types of medication are approved for treating tobacco use disorder in adults: nicotine replace-

ment, bupropion, and varenicline. A number of randomized trials have evaluated medications, usually in combination with psychosocial therapies, for smoking cessation in adolescents and young adults. A meta-analysis found that pharmacotherapy resulted in increased abstinence in the short term, but had no effect on long-term abstinence. The most promising clinical trial results have been with bupropion, but even these findings have been mixed. The trials suggest that an adequate dose, 300 mg/day, is required to achieve abstinence from smoking and that bupropion may enhance the effectiveness of contingency management for smoking cessation. Treatment adherence has been low in studies of adolescent smokers, and there has been little research on alternative nicotine and tobacco products in young people.

Several clinical trials support the efficacy of buprenorphine for opioid use disorder, and it is the only FDA-approved medication for any adolescent substance use disorder (opioid use disorder in patients aged ≥16 years). Interpretation of the existing buprenorphine trials is limited by a lack of patient diversity, high relapse rates, and other problems. Methamphetamine use is rare in adolescents and correspondingly poorly studied; a single pilot study showed disappointing results with bupropion.

Squeglia L, Fadus M, McClure E, Tomko R, et al: Pharmacological treatment of youth substance use disorders. *Journal of Child and Adolescent Psychopharmacology* 2019;29:559–572. doi 10.1089/cap.2019.0009. From the Medical University of South Carolina, Charleston. **Funded by the National Institute on Alcohol Abuse and Alcoholism; and other sources. One of 5 study authors disclosed a potentially relevant financial relationship; the remaining authors declared no competing interests.**

Common Drug Trade Names*: buprenorphine—*Subutex*; bupropion—*Zyban*; naltrexone—*ReVia*; ondansetron—*Zofran*; topiramate—*Topamax*; varenicline—*Chantix

Theta Burst Stimulation for Depression

In a preliminary study, theta burst stimulation (TBS) was feasible, well tolerated, and effective in adolescents and young adults with treatment-resistant depression. In adults, TBS appears to be at least as effective as repetitive transcranial magnetic stimulation (rTMS), and treatment requires a fraction of the time.

Methods: Study subjects, aged 16–24 years, had a diagnosis of major depression, a 17-item Hamilton Rating Scale for Depression (HAM-D) score of ≥20, and had undergone ≥1 unsuccessful antidepressant trial during the current episode. Patients were scheduled to receive intermittent TBS to the left dorsolateral prefrontal cortex (DLPFC) and continuous TBS to the right DLPFC at 80% of the active motor threshold 5 days/week for 2 weeks. The primary efficacy outcomes were change in HAM-D score after 5 sessions and at the end of treatment.

Results: A total of 20 patients entered the trial, all received and tolerated ≥6 TBS treatments, 18 completed all 10 treatments, and 17 completed the final evaluation. Most patients (n=13) met criteria for treatment resistance (i.e., ≥2 failed antidepressant trials). At baseline 14 patients were receiving medication, which was required to be unchanged for ≥4 weeks before study entry.

Decreases in depression occurred in 19 of the 20 patients, including 2 of the 3 who did not complete treatment. Average HAM-D scores decreased from 22.4 at baseline to 17.1 after session 5 (effect size,* 1.18; $p<0.001$) and further to 13.5 after session 10 (effect size,1.86; $p<0.0001$). After the 10th treatment, 2 patients achieved remission (HAM-D <7) and 2 others met criteria for response (≥50% reduction in HAM-D score). Higher levels of anhedonia at baseline were associated with a lower likelihood of response.

A total of 17 patients were experiencing suicidal ideation at baseline. After treatment, 9 patients reported suicidal ideation, although at a lower mean intensity than before. Headache, reported

at least once by 13 patients, was the most common adverse event. Other adverse effects, which were generally mild, included chest tightness, scalp pain, anxiety, nausea, GI symptoms, nasopharyngitis, and general discomfort.

Discussion: Although these results are positive, the study had a small sample size and short duration. Larger, longer-term, sham-controlled studies appear to be warranted.

Dhami P, Knyahnytska Y, Atluri S, Lee J, et al: Feasibility and clinical effects of theta burst stimulation in youth with major depressive disorders: an open-label trial. *Journal of Affective Disorders* 2019;253:66-73. doi 10.1016/j.jad.2019.07.084. From the Centre for Addiction and Mental Health, Toronto, Canada; and other institutions. **Funded by the Canadian Institutes of Health Research; and other sources. The authors declared no competing interests.**

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First-Line Behavioral Treatment for ADHD

In a randomized trial, children with ADHD who received a first-line behavioral intervention were half as likely to receive treatment with methylphenidate (*Ritalin*) during the school year as those who received no behavioral intervention. The 2 treatment groups had similar symptom outcomes by the end of the school year, and treatment costs were comparable.

Background: There are 3 established evidence-based treatments for ADHD—medication, behavioral treatment, and the combination—but many questions remain about timing and intensity of treatment. This study was designed to address uncertainties about the optimal sequencing of these treatments, their relative costs, the efficacy of high- versus low-intensity behavioral interventions, and whether treatment outcomes are influenced by factors such as patient age and externalizing disorders.

Methods: The study was conducted in children who had participated in a summertime randomized study in a model camp setting. Participants, aged 5–13 years, with DSM-IV ADHD, were exposed to 3 weeks each of randomized no, low-, and high-intensity behavioral treatment, crossed with placebo or 2 dosages of methylphenidate, for a total of 9 weeks. All parents participated in an 8-week course of large-group training.

The present study commenced at the start of the following school year. Children not taking stimulant medication were randomly assigned to high-intensity, low-intensity, or no behavioral treatment, applied throughout the school year. Behavioral treatment consisted of consultant visits to set up school- and home-based daily report cards, a bank of additional consultations available, and the option for parents to attend additional training booster sessions. The main difference between the high- and low-intensity conditions was the number of available consultations to parents and teachers and access to help with interventions such as school-based rewards, escalating time-outs, and point systems. Participant behavior and need for additional treatment were rated weekly by teachers and parents and reviewed by study staff. If the student had 3 weekly ratings indicating a need for additional treatment, a medication assessment was completed. If medication was deemed necessary, treatment with immediate-release methylphenidate was initiated in the school setting first; home-based medication was considered if subsequent parent ratings indicted continued impairment.

Results: A total of 116 families participated in the school-year study. Parents and teachers assigned to the high-intensity behavioral program did not use the extra consultations and booster trainings to which they had access. Therefore the high- and low-dose groups were merged for analysis. Children assigned to behavioral consultation were about half as likely as their peers to start methylphenidate both in school and at home during each week of the school year (hazard ratios,* 0.53 and 0.43, respectively). Increased age was associated with a reduced probably of starting methylphenidate. Parental education, previous medication use

at home, and comorbid oppositional defiant disorder or conduct disorder were not associated with likelihood of starting medication.

The median time to receipt of medication at school by 50% of patients was 5 weeks among those who did not receive behavioral consultation, compared with 18 weeks for those did. At the end of the school year, 63% of the behavioral consultation group and 81% of controls were receiving medication during the school day, a statistically nonsignificant difference. Rates of medication use at home were 26% and 63%, respectively, also a nonsignificant difference. Patients who received behavioral consultation were taking somewhat lower stimulant doses on average (0.32 versus 0.41 mg/kg; p=ns). Compared with children in the behavioral treatment group, over the school year children who did not receive behavioral consultation consumed 75% more methylphenidate. Teachers and parent rated both groups similarly on symptoms of inattention/overactivity and oppositional/defiance.

An economic comparison, based on the costs of generic immediate-release drug formulations and time spent by physicians, therapists, teachers, and parents, found total treatment costs were significantly lower in the group that did not receive behavioral therapy. However, when the cost calculations were repeated based on the price of present-day extended-release formulations, which may be more representative of current practice, the overall costs were similar in those who did and did not receive behavioral therapy.

Discussion: These results suggest that the use of relatively low-intensity behavioral interventions can reduce cumulative methylphenidate exposure by delaying the use of medication, decreasing the required dose at school, and reducing the prevalence of use at home. The finding that only about one-quarter of children required medication at home raises questions about the widely adopted practice of daily, extended-release dosing regimens to cover evening/home hours.

Coles E, Pelham III, W, Fabiano G, Gnagy E, et al: Randomized trial of first-line behavioral intervention to reduce need for medication in children with ADHD. *Journal of Clinical Child & Adolescent Psychology* 2019; doi 10.1080/15374416.2019.1630835. From Florida International University, Miami; and other institutions. **Funded by the NIMH; and other sources. The authors declared no competing interests.**

***See Reference Guide.**

ADHD and Hypomania: Genetic Risks

Results of a twin study of genetic risk factors for ADHD and hypomania provide additional evidence for the symptom overlap between the 2 disorders while supporting the distinction between the diagnoses.[1]

Methods: The analysis was part of a longitudinal study of Swedish monozygotic or dizygotic twin pairs. ADHD symptoms were assessed using parent-rated instruments when children were aged 9, 12, 15, and 18 years. Hypomania was assessed at ages 15 and 18 years, also using parent ratings. Additional information about diagnosis and treatment of ADHD and bipolar disorder was obtained from national administrative databases. The potential association of genetic and environmental risk factors for ADHD and hypomanic symptoms was assessed using classic twin study methods comparing monozygotic and dizygotic twins.

Results: More than 13,500 twin pairs were assessed at ages 9 or 12 years, nearly 3,800 pairs were available for follow-up at age 15 years, and about 3,000 pairs at age 18 years. ADHD symptoms before age 13 years were significantly associated with hypomania symptoms at ages 15 and 18 years (β-coefficients,* 0.3 and 0.19, respectively; $p<0.001$ for both). Removing items that were similar between the 2 disorders did not change this association. Among 52 individuals with a diagnosis of bipolar disorder, 37% also had a diagnosis of ADHD, compared with 4% of those without bipolar disorder ($p<0.001$).

Moderate-to-strong heritability was found for ADHD and hypomania traits. Genetic factors shared with ADHD accounted for about 13–29% of the variance in hypomania traits at ages 15 18 years. Nonshared, hypomania-specific genetic risk factors accounted for 25–42% of the variance in hypomania. Nonshared environmental factors played a negligible role in hypomania. Of the subtypes of ADHD symptoms, hyperactivity-impulsivity was more strongly associated with hypomanic symptoms than inattention.

Editorial: The diagnostic definition of pediatric bipolar disorder is evolving, and differentiating this disorder from ADHD can be difficult.[2] The study results do not account for mood-related symptoms (e.g., temper outbursts, mood reactivity, and irritability), which are not diagnostic criteria for ADHD, but that commonly occur. Further complicating matters is the new DSM-5 entity, disruptive mood dysregulation disorder (DMDD), which may apply to many children previously determined to have bipolar disorder. Regardless of the complex diagnostics, early identification and recognition of comorbidity is essential given the more severe disease course and potential negative outcomes associated with ADHD–bipolar disorder comorbidity (e.g., suicide attempts).

[1]Hosang G, Lichtenstein P, Ronald A, Lundstrom S, et al: Association of genetic and environmental risks for attention-deficit/hyperactivity disorder with hypomanic symptoms in youths. *JAMA Psychiatry* 2019; doi 10.1001/jamapsychiatry.2019.1949. From the University of London, U.K.; and other institutions. **Funded by the Karolinska Institute; and other sources. One of 5 study authors disclosed potentially relevant financial relationships; the remaining authors declared no competing interests.**

[2]Moran L, Guvenek-Cokol P, Perlis R: Attention-deficit/hyperactivity disorder, hypomania, and bipolar disorder in youth [editorial]. *JAMA Psychiatry* 2019; doi 10.1001/jamapsychiatry.2019.1926. From McLean Hospital, Belmont, MA; and other institutions. **Two of 3 authors disclosed potentially relevant financial relationships; the remaining author declared no competing interests.**

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Beta-Coefficient: Used in logistic regression analysis, the β-coefficient represents the degree of change in the outcome variable for every 1-unit of change in the predictor variable.

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). The rating checklists are posted at www.alertpubs.com.