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Mood Disorders: School-Based Prevention

Educational settings are at the forefront of prevention initiatives for common mental disorders in young people. However, a systematic review and network meta-analysis found no evidence supporting the effectiveness of school-based interventions to prevent depression or anxiety.[1] An accompanying editorial argues that based on study limitations, the conclusion that school-based programs are not helpful is potentially premature.[2]

Methods: The systematic review included all randomized and quasi-randomized trials in participants aged 4–18 years attending full- or part-time education programs. Interventions could include any psychological, psychosocial, educational, or physical programs that were implemented in an educational setting. Universal and targeted interventions were both included as long as the explicit aim was to prevent anxiety or depression. Studies in which >40% of subjects had a diagnosed mental health disorder were excluded, as were studies of programs targeting stress, bullying, or substance abuse, and those addressing specific life events. The primary study outcomes were self-reported depression or anxiety, wellbeing, or suicidal behavior or self-harm, measured at the end of treatment and in some studies at longer-term follow-up. Post-hoc subgroup analyses were conducted to identify any potential inequalities according to sex, ethnicity, and socioeconomic status. The network meta-analysis included 4 types of control intervention: none; waitlist; usual curriculum; and attention.

Results: The review identified 137 studies with 56,620 participants. Slightly more than half of the study interventions (n=76) were classified as universal and the remaining 61 as targeted. Of the latter group, 51 (84%) were selective (conducted in high-risk groups) and 10 were indicated (in individuals in high-risk groups and showing subthreshold symptoms). The prevention focus was anxiety in 30% of studies, depression in 45%, and both conditions in 25%. The most commonly investigated intervention was cognitive-behavioral therapy (103 studies), followed by a relaxation or mindfulness-based intervention (11 studies). Small numbers of studies evaluated interpersonal therapy, a third-wave intervention, behavioral interventions, biofeedback, exercise, bias modification, or occupational therapy. Most interventions (96%) were delivered to whole classrooms or smaller groups, most often by a

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person external to the educational setting, usually a mental health professional. The average duration of intervention was about 11 hours.

There was high heterogeneity and therefore uncertainty in estimates of treatment effects, such that the authors could not recommend any 1 type of intervention as the most effective for preventing anxiety or depression. Evidence supported a small effect of CBT on anxiety prevention in universal settings. No intervention was effective in preventing anxiety or depression in targeted primary-school settings. Exercise was moderately effective at reducing anxiety in targeted secondary-school settings. Third-wave CBT-based treatments appeared to be effective at preventing depressive symptoms, but the estimate was based on a single trial in a targeted setting.

Small sample sizes precluded subgroup analyses by sex and ethnicity. Prevention was more effective in higher socioeconomic class settings in secondary schools only. There were also insufficient data to analyze the outcomes of wellbeing, suicidality, or self-harm.

Editorial. The present findings must be interpreted cautiously in light of several important limitations. First, study populations included mixed samples of patients with and without existing mental health disorders and interventions could be aimed at treatment of an existing disorder or prevention of new onset. In addition, other outcomes that might be improved by the interventions, such as educational performance, future employment, and risk-taking behavior were not evaluated, and programs targeting relevant areas such as bullying, mental health promotion, and managing specific events were excluded. School-based mental health promotion is evolving to embrace a broader definition of mental health and a wider spectrum of providers, and use of programs targeting different levels of need and multi- dimensional programs is becoming more widespread. However, these were excluded from the meta-analysis, which could lead to a misrepresentation of the overall effects of school-based intervention.

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

[1]Caldwell D, Davies S, Hetrick S, Palmer J, et al: School-based interventions to prevent anxiety and depression in children and young people: a systematic review and network meta-analysis. *Lancet Psychiatry* 2019;6 (December): 1011–1020. doi 10.1016/S2215.0366(19)30403-1. From the University of Bristol, U.K.; and other institutions. **Funded by the U.K. National Institute for Health Research. Seven of 13 study authors disclosed potentially relevant financial relationships; the remaining authors declared no competing interests.**

[2]Fazel M, Kohrt B: Prevention versus intervention in school mental health [Editorial]. *Lancet Psychiatry* 2019;6 (December): 969–971. doi 10.1016/S2215.0366(19)30440-7. From The University of Oxford Warneford Hospital, U.K.; and George Washington University, Washington, D.C. **The authors declared no competing interests.**

***See Reference Guide.**

Antidepressant Tolerability in OCD, Anxiety Disorders

According to the results of a meta-analysis, adverse events differ between SSRIs and SNRIs in children and adolescents with anxiety disorders or OCD. Several of the most common adverse effects are more likely to occur with SSRIs, while SNRIs have a similar incidence to placebo for most events. Neither medication class was associated with suicidality.

Methods: All randomized, placebo-controlled, parallel-group trials of an SSRI or SNRI in the treatment of OCD or social, generalized, or separation anxiety disorder in patients aged ≤18 years were identified in the literature. Relative risks were calculated for common adverse effects (i.e., abdominal pain, activation, diarrhea, nausea, insomnia, headache, and sedation) and for discontinuation because of adverse effects. A total of 18 trials, comprising >2600 participants, and evaluating 4 SSRIs (i.e., fluoxetine, fluvoxamine, paroxetine, sertraline) and 3 SNRIs (i.e., atomoxetine, venlafaxine, duloxetine) were identified and included.

Results: Compared with placebo, SSRIs were associated with significantly higher rates of abdominal pain (relative risk [RR],* 1.53; p=0.005), activation (RR, 2.39; p=0.003), headache (RR, 1.24; p=0.04), insomnia (RR, 1.93; p=0.001) and sedation (RR, 1.94; p=0.024). Only the rate of nausea was significantly higher with SNRIs than with placebo (p=0.002). With the exception of activation in the combined anxiety/OCD population (RR, 1.32; p=0.007), no individual adverse event occurred significantly more frequently with SSRIs than with SNRIs.

Treatment-emergent suicidality did not differ between SSRIs and placebo or between SSRIs and SNRIs in patients with anxiety, OCD, or the combined patient population. SSRIs were associated with a higher rate of adverse event-related discontinuation than placebo (RR, 3.59; p=0.0003), while SNRIs were not.

Discussion: SSRIs are known to have superior efficacy to SNRIs and are the treatment of choice for pediatric anxiety. However, the present results suggest that young patients are more likely to experience activation, which can increase drug discontinuation and decrease treatment response, with SSRIs than with SNRIs.

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

Mills J, Strawn J: Antidepressant tolerability in pediatric anxiety and obsessive-compulsive disorders: a Bayesian hierarchical modeling meta-analysis. *Journal of the American Academy of Child and Adolescent Psychiatry* 2019; doi 10.1016/j.jaac.201910.013. From the University of Cincinnati and the Cincinnati Children's Medical Center, OH. **Funded by the Eunice Kennedy Shriver National institute of Child Health and Development; and other sources. One study author disclosed potentially relevant financial relationships; the remaining author declared no competing interests.**

Common Drug Trade Names*:** **atomoxetine—*Strattera;* duloxetine—*Cymbalta*; fluoxetine—*Prozac*; fluvoxamine—*Luvox*; paroxetine—*Paxil*; sertraline—*Zoloft*; venlafaxine—*Effexor

***See Reference Guide.**

AR19 Amphetamine Bioequivalence

Results of 3 clinical studies support the bioequivalence of racemic amphetamine sulfate (*Evekeo*) and AR19—an investigational formulation of immediate-release amphetamine designed to deter manipulation for nonoral use.

Background: Prescription stimulants have a high potential for nonmedical use, including misuse and abuse, in part because of their euphoric effects and the enhanced alertness associated with their use. Nonoral routes of administration are frequently reported with nonmedical stimulant use. AR19 has been developed with technology that impedes manipulation of the pellets in the capsules for intranasal, intravenous, or smoking routes of administration.

Methods: Arbor Pharmaceuticals, the manufacturer of AR19, conducted 3 separate randomized crossover studies (i.e., bioequivalence, dose comparison, and food effect) to assess the investigational formulation. All 3 studies included healthy adults, aged 18–45 years, with a body mass index of 18–30 kg/m^2. The bioequivalence study included 36 participants (16 women) who received 20 mg of either AR19 or racemic amphetamine sulfate followed by crossover to the alternate medication. In the dose comparison study, 24 participants (16 women) were randomized to receive either 5 or 30 mg AR19 followed by the alternate dose. The 36 food effect study participants (22 women) received 20 mg AR19 as intact capsule while fasted or after high fat/calorie meal and as pellets sprinkled on applesauce or yogurt. In all study periods, blood samples were analyzed for dextroamphetamine (d-AMP) and levoamphetamine (l-AMP) pharmacokinetic parameters (e.g., bioavailability, peak concentrations, time taken to reach the maximum concentration).

Results: Pharmacokinetics of AR19 and racemic amphetamine were equivalent, as were values with intact capsule and sprinkled AR19 pellets in the fasted and meal conditions. Additionally,

bioavailability was similar at doses of 5 and 30 mg and was not impacted by meal consumption or sprinkling on food. Common adverse effects of AR19 included headache; palpitations; nausea; increased energy; disturbance in attention; dizziness; psychomotor hyperactivity; euphoric mood; dry mouth; asthenia; jitteriness; dystonia; and agitation. Most adverse effects were mild and affected only a single patient each. No serious adverse events were reported.

Discussion: Taken together, the results of these 3 studies suggest that AR19 has the potential to serve as an alternate option to racemic amphetamine, particularly in patients for whom the potential of nonmedical stimulant use is a concern.

Caras S, Sharpe T: Pharmacokinetics of AR19, an immediate-release amphetamine sulfate formulation designed to deter manipulation for administration via nonoral routes: bioequivalance to reference racemic amphetamine sulfate, dose proportionality, and food effect. *Journal of Child and Adolescent Psychopharmacology* 2019; doi 10.1089/cap.2019.0133. From Arbor Pharmaceuticals Atlanta, GA. **Funded by Arbor Pharmaceuticals. Both study authors disclosed financial relationships with Arbor.**

Brain Imaging in First-Episode Psychosis

American Psychiatric Association guidelines recommend the use of brain imaging in the evaluation of patients with first-episode psychosis. However, according to the results of a retrospective cohort study, routine neuroimaging does not have significant diagnostic value and does not impact clinical management of these patients.

Background: The distinction between primary and secondary psychosis may have important treatment implications. Structural abnormalities, which can be uncovered via neuroimaging, are a potential etiological factor in secondary psychosis. However, radiation from CT scans is an important consideration for young patients, and guidelines for other neurological conditions aim to limit the number of unnecessary MRI scans.

Methods: Charts were retrospectively reviewed for patients aged 15–24 years who were referred to an early psychosis intervention program in Canada over nearly 2 decades. All patients underwent MRI or CT scans as part of the diagnostic evaluation for first-episode psychosis. Positive scans were those with findings that caused a change in the clinical management of the patient. Incidental findings were not deemed related to psychosis and did not change patients' clinical management.

Results: A total of 443 patients were referred for evaluation; 351 underwent CT scan, 63 received an MRI, and 29 underwent both types of imaging. Incidental findings (e.g., arachnoid cyst, calcification, nonspecific hypodensity or hyperintensity) were present in 25 of the 443 scans (5.6%). These incidental findings lead to a follow-up scan in 11 patients. None of the neuroimaging findings were considered causal or contributory to secondary psychosis, and none required urgent follow-up or neurointervention.

Discussion: Although schizophrenia is associated with brain abnormalities (e.g., ventricular enlargement, loss of temporal lobe matter) that are present at onset of the disease, clinical neuroimaging does not specifically assess these factors. The present results suggest that neither MRI nor CT should be included in the routine workup of first-episode psychosis unless specifically indicated by the presence of an abnormal neurologic examination. In cases where imaging appears to be warranted, MRI may be the modality of choice as it avoids radiation exposure and produces better gray–white matter differentiation.

Andrea S, Papirny M, Raedler T: Brain imaging in adolescents and young adults with first-episode psychosis: a retrospective cohort study. *Journal of Clinical Psychiatry* 2019; doi 10.4088/JCP.18m12665. From McMaster University; and the University of Calgary, Canada. **Funded by the University of Calgary. The authors declared no competing interests.**

Revised AAP Guideline for Managing ADHD

Given the nationwide shortage of mental health specialists, pediatricians and other primary-care clinicians are increasingly called upon to care for young patients with mild-to-moderate ADHD. The American Academy of Pediatrics (AAP) has revised its clinical practice guideline for ADHD in children and adolescents to reflect recent research and the introduction of DSM-5. Key action statements have been updated and the guideline includes a revised process of care algorithm and recommendations about overcoming systemic barriers to the care of children and adolescents with ADHD.

AAP key action statements on the diagnosis, treatment, and monitoring of ADHD

1. Evaluate for ADHD any child or adolescent aged 4–18 years who presents with academic or behavioral problems and symptoms of inattention, hyperactivity, or impulsivity.
2. Determine that DSM-5 criteria have been met, including documentation of symptoms and impairment in >1 major setting with information obtained from parents or guardians, teachers, other school personnel, and mental health clinicians, and rule out any alternative cause.
3. Screen for comorbid conditions, including emotional or behavioral conditions, developmental conditions, and physical conditions.
4. Because ADHD is a chronic condition, manage children and adolescents with ADHD in the same manner as patients with special health care needs, following the principles of the chronic care model and the medical home.
5. For preschool-aged children, evidence-based parent training and/or behavioral classroom interventions should be used as first-line of treatment. Methylphenidate may be considered if these interventions do not provide significant improvement and there is at least moderate disturbance in functioning.

   For elementary and middle school-aged children with ADHD, prescribe approved medications along with parent training and/or behavioral classroom intervention.

   For older adolescents, prescribe FDA-approved medications (with the patient's agreement) along with evidence-based training interventions and/or behavioral interventions.

   For all patients attending school, educational interventions and individualized instructional supports, including school environment, class placement, instructional placement, and behavioral supports, are a necessary part of the treatment plan.
6. Titrate medication doses to achieve maximum benefit with tolerable side effects.
7. Initiate treatment of comorbid conditions or make a referral to an appropriate subspecialist for treatment. In some cases, treating ADHD may resolve or substantially improve comorbid conditions.

The guideline also identifies areas that require further research. These focus on creating new or improved processes for developmentally appropriate assessment of ADHD in

preschoolers; assessment of common comorbidities and functional impairment; and monitoring improvement over time (including determination of an optimal monitoring schedule). In addition, research is needed to further evaluate medication efficacy across age groups; off-label use of medications and other therapies; adverse effects of medication combinations; and effectiveness of school-based interventions. Finally, to provide effective collaborative care, methods to involve parents and patients in their own care; improvements to systems for communicating with schools, mental health professionals, and other community agencies; and electronic and web-based treatment aids are needed.

Wolraich M, Hagan Jr J, Allan C, Chan E, et al: Clinical practice guideline for the diagnosis, evaluation, and treatment of attention-deficit/hyperactivity disorder in children and adolescents. *Pediatrics* 2019;144(4):e20192528. doi 10.1542/peds.2019-2528. From the University of Oklahoma, Oklahoma City; and other institutions. **This guideline was compiled without external funding. Four of 17 study authors disclosed potentially relevant financial relationships; the remaining authors declared no competing interests.**

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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).

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