

CHILD & ADOLESCENT PSYCHIATRY ALERTS

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Saffron Extract for Anxiety and Depression

In a manufacturer-sponsored controlled trial, a standardized saffron extract (*affron*) reduced self-reported anxiety and depression symptoms in adolescents.

Methods: Study participants, aged 12–16 years, with anxiety or depression were recruited from the community through social and conventional media. Symptoms were assessed using the Revised Child Anxiety and Depression Scale (RCADS), and adolescents were included in the study if they had mild-to-moderate symptoms (i.e., scores >60th population-standardized percentile and below the 90th percentile on the total RCADS or on a subscale). Patients engaging in self-harm or with suicidal thoughts were excluded. Study participants were randomly assigned to receive a twice-daily standardized saffron extract in tablet form or placebo for 8 weeks. The primary outcome was change from baseline on the self-report RCADS. Parent-reported symptom scores were a secondary outcome.

Results: The 80 study participants had a mean age of 14 years, and about one-third were male. Of those enrolled, 12 patients withdrew from the study, most often because of refusal to take the tablets (n=5), worsening mental health (n=2), or commencement of other treatment (n=2). Discontinuation rates did not differ between treatment groups.

Saffron extract produced a larger reduction than placebo in youth-reported RCADS total anxiety scores and total internalizing scores, with effect sizes* of 0.58 and 0.61, respectively. Adolescents who received saffron demonstrated significantly larger improvements than the placebo group on several of the RCADS subscales including depression (p=0.016; effect size, 0.60), separation anxiety (p=0.003; effect size, 0.62), and social phobia (p=0.023; effect size, 0.58). Differences in generalized anxiety improvement also favored saffron but did not reach statistical significance (p=0.067; effect size, 0.44). Effect sizes were in the small-to-medium range. Parents of adolescents who received saffron also reported numerically larger improvements in their children's symptoms than those who received placebo, but these differences were smaller and not statistically significant.

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Participants who received saffron had a 33% mean reduction in total internalizing symptoms, compared with a 17% reduction with placebo ($p=0.029$). Rates of response, defined as a $\geq 50\%$ reduction in total internalizing symptoms, were 37% with saffron and 11% with placebo (odds ratio,* 4.81; $p=0.014$).

Discussion: The beneficial effects of saffron in the present study were smaller than those previously reported in the adult literature. However, the adult studies were conducted in patients with major depressive disorder, possibly accounting for some of the difference in effect sizes. The mechanisms of action of saffron are uncertain but may include antioxidant and anti-inflammatory effects, reduction of plasma corticosterone, and increases in brain concentrations of dopamine (without affecting serotonin or norepinephrine). Studies longer than 8–12 weeks in duration have not been conducted in adults or young patients, leaving the long-term efficacy of saffron extract undetermined.

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

Lopresti A, Drummond P, Inarejos-Garcia A, Prodanov M: affron®, a standardised extract from saffron (*Crocus sativus* L.) for the treatment of youth anxiety and depressive symptoms: a randomised, double-blind, placebo-controlled study. *Journal of Affective Disorders* 2018; doi 10.1016/j.jad.2018.02.070. From Murdoch University, Perth, Australia; and other institutions. **Funded by Pharmactive Biotech Products SL. The authors did not include disclosure of potential conflicts of interest.**

*See Reference Guide.

Marijuana Legalization and Adolescent Health

Survey data suggest that Colorado's legalization of medical marijuana in 2009, followed by recreational use in 2014, was not accompanied by increased use of the drug by adolescents. However, the number of marijuana-related emergency and urgent-care visits to a Colorado pediatric hospital increased nearly 5-fold in subsequent years.

Methods: To assess the effect of legalization on one facet of adolescent health, the investigators examined data from admissions to the emergency and urgent-care facilities of a tertiary-care children's hospital system in the Denver metropolitan area. Data were collected from visits between 2005 and 2015 by patients aged 13–20 years with a discharge diagnosis of marijuana/cannabis use or with a positive toxicology screen for tetrahydrocannabinol (THC). Urine drug screens were mandatory for patients admitted for behavioral health disorders.

Results: A total of 4202 marijuana-related visits occurred in patients with a mean age of 16 years (54% male) during the study years. The annual total increased steadily over the years, from 161 in 2005 to 777 in 2015. The number of behavioral health evaluations, which were provided for 67% of patients, also showed a steady increase from 84 in 2005 to 500 in 2015. The majority of patients received a diagnosis of cannabis use/abuse/misuse (62%) or substance abuse (33%). Comorbid psychiatric diagnoses were also common and included depression (39%), mood disorder (22%), conduct disorder (13%), anxiety/panic disorder (13%), ADHD (12%), bipolar disorder (6%), schizophrenia (5%), and "other" (31%).

Rates of marijuana-related visits, relative to all emergency/urgent care visits, were compared for 2009 and 2015, the first full years of medical and recreational marijuana legalization, respectively. The frequency increased from 1.8 per 1000 visits in 2009 to 4.9 per 1000 in 2015. Marijuana-related behavioral health consultations increased from 1.2 per 1000 visits in 2009 to 3.2 per 1000 visits in 2015.

Discussion: Although there has been an increase in the frequency of urine drug screens overall, this does not fully account for the increase in cannabis-related visits. These data should prompt concern now that more than half of states have legalized at least some type

of marijuana use, in part because adolescents' risk perception of marijuana may have decreased, even if data do not consistently show an increase in actual use.

Wang G, Davies S, Halmo L, Sass A, et al: Impact of marijuana legalization in Colorado on adolescent emergency and urgent care visits. *Journal of Adolescent Health* 2018; doi 10.1016/j.jadohealth.2017.12.010. From the University of Colorado Anschutz Medical Campus; and Children's Hospital Colorado, Aurora, CO. **This research was conducted without specific funding. One of 5 study authors disclosed potentially relevant financial relationships; the remaining authors declared no competing interests.**

Treating Anxiety in Emerging Adulthood

The period of emerging adulthood can be complicated by the presence of anxiety disorders, in part because the developmental tasks of young adulthood are dependent on abilities, such as emotional regulation and social skills, which are often deficient in persons with anxiety or other psychiatric disorders. A newly developed cognitive-behavioral treatment program, the Launching Emerging Adults Program (LEAP), has been designed specifically for young adults with anxiety disorders and their families.

Emerging adulthood spans the years of age 18 to 25, approximately. Developmental milestones during this period usually include growth of self-identity, financial independence from parents, management of personal self-care, completion of education, and establishment of long-term relationships. Anxiety disorders are highly prevalent during these years, affecting from 12% to >25% of young adults in different cross-sectional studies. The transition to early adulthood is associated with a dramatic increase in the prevalence of anxiety disorders, most often as an extension of anxiety in childhood and adolescence. Cognitive behavioral therapy (CBT) is a well-supported treatment for anxiety disorders in children and adolescents. However, recent research suggests the effects of CBT are less robust in adolescence than in childhood, and its effects in these age groups may not be lasting.

The LEAP model of CBT was designed specifically for emerging young adults with anxiety and their families. LEAP targets individual factors that maintain anxiety and delays or deficits in life skills. The therapy also addresses parental behaviors that often interfere with the developmental tasks of young adulthood. The schedule includes both individual and family sessions plus group-based exposure sessions with peers. The program can be adapted flexibly, allowing for more intensive family work for low-functioning patients who live at home and are not employed or in school, or for little or no family involvement if the patient is living independently. The therapy is organized into 4 stages, with a flexible total of about 22 sessions.

Phase 1. The first 4 sessions heavily involve the family and focus on psychoeducation and identifying the patient's current level of function. In these sessions, the roles of avoidance and parent involvement in maintaining anxiety are addressed. Both patients and parents are provided with an instrument to track response to anxiety-provoking situations. This phase also includes goal setting and creation of a hierarchy of anxiety-provoking situations.

Phase 2. In sessions 5–10, responsibility for treatment and clinical focus are shifted to the patient. With less family involvement, the patient is taught cognitive restructuring and problem-solving skills. Role playing and behavioral experiments are incorporated to challenge anxiety-related negative predictions. Skill deficits and emotion dysregulation can be addressed using assertiveness and social-skills training, and patients are taught general affect regulation, relaxation, self-soothing, and problem solving. Communication skills and family problem-solving strategies are incorporated in the final session of this phase, attended by patients and parents, to facilitate independent functioning.

Phase 3. The third stage includes 2 types of peer-group experiences: group-based exposure to challenging situations, and optional "adulting" groups designed to help low-functioning

patients. Group exposures are offered at beginner, intermediate, and advanced levels and are designed to reduce avoidance of challenging situations and to improve coping skills. Patients test new skills, practice problem solving, and give and receive peer support. The "adulting" group is an optional short-term intensive program that meets several days per week for 2–3 weeks. It is intended to increase confidence and competence in completion of daily adult responsibilities and habits.

Phase 4. The final phase is aimed at solidifying gains, transitioning to the adult role, and preventing relapse. In the final patient–parent session, behavioral contracts are created to clearly define the responsibilities of each family member and to set goals for role transitions. The program concludes with several sessions promoting continued anxiety management and information on how to access posttreatment support.

In contrast to many existing anxiety therapies, LEAP directly addresses the patient's functional status and family framework while providing skill-building and exposure. Although the present report does not address efficacy of the program, testing of the model is ongoing along with development of potential uses of virtual reality environments to enhance contextual cues.

Hoffman L, Guerry J, Albano A: Launching Anxious Young Adults: a specialized cognitive-behavioral intervention for transitional aged youth. *Current Psychiatry Reports* 2018; doi 10.1007/s11920-018-0888-9. From Columbia University Medical Center, New York, NY; and other institutions. **Source of funding not stated. One study author disclosed a potentially relevant financial relationship; the remaining 2 authors declared no competing interests.**

Pediatric Asenapine

Asenapine (*Saphris*) is a novel antipsychotic, approved in the U.S. as monotherapy for bipolar I disorder in children and adolescents aged 10–17 years. Approval was based on a single, 3-week, randomized, placebo-controlled trial. A 50-week open-label extension study provided additional safety and efficacy data. The manufacturer of asenapine also sought regulatory approval for treatment of pediatric schizophrenia. Drug effects did not differ significantly from placebo in the acute trial, and approval was not granted; however, an extension trial provided additional safety data. The drug was well tolerated in acute and long-term studies for both indications. Serious adverse events were generally related to worsening of the underlying psychiatric disorder. The most common treatment-emergent adverse events were somnolence, sedation, and oral symptoms. In the extension studies, weight gain was reported as an adverse event in 18% of study patients with bipolar disorder and about 14% of those with schizophrenia. Suicidal ideation was reported in patients with both bipolar disorder and schizophrenia, mostly limited to those who had a history of ideation. Extrapyramidal symptoms affected $\geq 5\%$ of patients with both disorders and were generally mild or moderate.

Asenapine shares the dopamine D₂ and serotonin 5-HT_{2a} receptor affinity of other second-generation antipsychotics, but also has a complex profile of activity at other receptors. It has high antagonist activity for multiple other dopamine and serotonergic receptors and for adrenergic and histamine receptors, moderate antagonist activity at the histamine H₂ receptor, and no apparent affinity for muscarinic receptors. These properties predict a low likelihood of anticholinergic effects but may cause sedation, weight gain, and cardiovascular effects. Asenapine is only available as a sublingual tablet, with 3 dose strengths. It must be dissolved under the tongue; bioavailability is markedly reduced if the tablet is swallowed. Pharmacokinetics are similar to those in adults, with a time to peak concentration of 1–2 hours and a time to steady state of about a week. Children and adolescents can take the recommended adult doses, but a short up-titration is recommended in pediatric patients to avoid dystonia and initial sensitivity. Eating and drinking should be avoided for 10 minutes after asenapine administration to prevent interference with mucosal absorption. In addition, consuming a high-fat meal immediately prior to sublingual asenapine administration can reduce drug exposure by as

much as 20%. Mouth and/or throat numbness or tingling may occur immediately after asenapine administration, but these sensations typically resolve within 1 hour. Somnolence and sedation may be treatment-limiting in some young patients.

Stepanova E, Grant B, Findling R: Asenapine treatment in pediatric patients with bipolar I disorder or schizophrenia: a review. *Pediatric Drugs* 2018;20 (April):121–134. From Johns Hopkins University; and other institutions, Baltimore, MD. **Funded by Allergan. Two of the 3 study authors disclosed potentially relevant financial relationships; the remaining author declared no competing interests.**

Aripiprazole vs Quetiapine: QT Effects

In a head-to-head, randomized comparison study, extended-release quetiapine was associated with small but statistically significant increases in the QTc interval in children and adolescents with first-episode psychosis while aripiprazole was not. The quetiapine-associated changes were small and not likely to be clinically significant but they do indicate a need for caution in patients with cardiac risk factors.

Methods: This analysis was part of a larger trial comparing the safety and efficacy of quetiapine and aripiprazole in patients aged 12–17 years with first-episode schizophrenia, psychotic disorders, mania or depression with psychotic symptoms, or related disorders. Participants were antipsychotic-naïve or had limited prior exposure to the drugs. After random assignment, quetiapine and aripiprazole were titrated using a standardized schedule to target dosages of 600 mg/day extended-release quetiapine and 20 mg/day aripiprazole; maximum permitted dosages were 800 mg/day and 30 mg/day, respectively. Patients received treatment for 12 weeks. ECGs were obtained before starting study medication and at weeks 4 and 12 of treatment. For this analysis, the primary outcome measure was the corrected QT interval (QTc). QT variability or dispersion (QTd) was measured as the difference between the maximum and minimum QTc intervals in 2 or 3 consecutive complexes in 5 or 6 leads.

Results: A total of 93 patients were included in the comparison of QTc and 49 in the analysis of QTd. Baseline values for these measurements did not differ between patients with or without prior exposure to antipsychotics. In patients who received quetiapine, the mean change in the QTc from baseline to 12 weeks was 6.8 ms ($p=0.025$). The increase was evident at the 4-week evaluation and did not increase further after that time. The QTc did not change significantly in aripiprazole-treated patients. A total of 4 patients in the quetiapine group experienced a QTc increase of >40 ms, but no patient had an increase beyond the commonly used cutoff for QTc prolongation of 450 ms. The magnitude of change in QTc was not affected by antipsychotic dose or by patient age, body mass index, or smoking status. Higher baseline potassium levels were associated with greater QTc change in the quetiapine group.

Mean QTd decreased, although nonsignificantly, in both groups by week 12 of treatment. Mean heart rate increased by 11 bpm in the quetiapine group and was unchanged with aripiprazole. Rates of dizziness and tachycardia were higher in the quetiapine group than the aripiprazole group, although the differences were not statistically significant.

Discussion: The QT changes with quetiapine found in the study were small and likely not clinically significant in otherwise healthy patients, however, they may be clinically relevant in patients with significant risk factors for cardiac arrhythmias (e.g., polypharmacy, family history) for whom aripiprazole may be a better option.

Jensen K, Gartner S, Correll C, Ruda D, et al: Change and dispersion of QT interval during treatment with quetiapine extended release versus aripiprazole in children and adolescents with first-episode psychosis: results from the TEA trial. *Psychopharmacology* 2018;235 (March):681–693. From the University of Copenhagen, Denmark; and other institutions. **Funded by the National Research Council for Health and Disease; and other sources. Two of 11 study authors disclosed financial relationships with commercial sources; the remaining authors declared no competing interests.**

Common Drug Trade Names: aripiprazole—*Abilify*; quetiapine, extended-release—*Seroquel XR*

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.

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.

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.

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