CHILD & ADOLESCENT PSYCHIATRY ALERTS

Volume XXI / July 2019 / Number 7 www.alertpubs.com

Saffron for ADHD

In a pilot study, *Crocus sativus L.* (saffron) was as effective as short-acting methylphenidate (*Ritalin*) in children with ADHD. The spice, commonly used in herbal medicine, could be an option for treatment of ADHD in patients whose families prefer nonstimulant or herbal therapy.

Background: Saffron is used in traditional medicine for its antispasmodic, antiseptic, antidepressant, anticancer, and anticonvulsant effects. It may inhibit dopamine and norepinephrine reuptake and act as an agonist at NMDA and GABA receptors. It also has antiinflammatory and free radical scavenging effects.

Methods: Study participants were outpatients, aged 6–17 years, with a DSM-5 diagnosis of ADHD and an ADHD Rating Scale IV (ADHD-RS-IV) score ≥1.5 standard deviations above age- and gender-based norms. Patients were randomly assigned to receive 6 weeks of double-blind, weight-based treatment with 20–30 mg/day methylphenidate or saffron administered in divided doses. The primary study outcome was change from baseline in the parent version of the ADHD-RS-IV.

Results: A total of 54 patients were randomized, 27 to each group. There were no significant baseline between-group differences in demographics or illness variables. Mean patient ages were 8 and 9 years in the saffron and methylphenidate groups, respectively, and 80% of patients were male. The mean baseline parent-rated ADHD-RS-IV score was 34 in both groups. By week 6, scores decreased to a mean of 10.5 points in both treatment groups. Results were similar for secondary outcomes including teacher-rated ADHD-RS-IV scores and reductions on the inattentive and hyperactive/impulsive subscales on both parent- and teacher-rated instruments. Response, defined as a ≥40% decrease in the parent-rated ADHD-RS-IV score was achieved by 25 patients in the saffron group and 24 in the methylphenidate group. Adverse events (e.g., headache, decreased appetite, insomnia) did not differ between the saffron and methylphenidate groups.

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

Baziar S, Aqamolaei A, Khadem E, Mortazavi S, et al: *Crocus sativus L.* versus methylphenidate in treatment of children with attention-deficit/hyperactivity disorder: a randomized, double-blind pilot study. *Journal of Child and Adolescent Psychopharmacology* 2019; doi 10.1089/cap.2018.0146. From Tehran University of Medical Sciences, Iran. **Funded by the university. The authors declared no competing interests.**

***See Reference Guide.**

CHILD & ADOLESCENT PSYCHIATRY ALERTS (ISSN 2640-8236) is published monthly by M.J. Powers & Co. Publishers, 45 Carey Avenue, Butler, NJ 07405. Telephone 973-898-1200. E-mail: child@alertpubs.com. Subscription $105 a year in the U.S.; $113.50 Canada; $123.50 elsewhere; $157 institutional. Subscribers may enroll in the 12-month CME program for an additional $83.00 per year, or enroll in the comprehensive, annual Self-Assessment program for $270 (in the U.S.). M.J. Powers & Co. Publishers is fully independent and accepts no commercial support of any kind.

Clinical Features of PANS

Pediatric acute-onset neuropsychiatric syndrome is a controversial disorder of unknown etiology and with no defined biomarkers. Although there are expert consensus guidelines on treatment, a lack of well-defined patient cohorts contributes to the uncertainty about the disorder. This report describes initial experience with a cohort of patients that will continue to accumulate and be followed to observe long-term outcomes.

Patients were recruited from a specialist clinic for pediatric obsessive-compulsive disorder and related conditions at the Karolinska Institute in Stockholm, Sweden. The clinic is a regional referral center for pediatric medical and psychiatric services. Referred patients and their parents or guardians complete detailed questionnaires and undergo thorough medical and psychiatric evaluations at the first clinic visit. Diagnoses are made according to the International Classification of Diseases, 10th Revision (ICD-10) and DSM-5. Patients treated at the clinic undergo follow-up evaluations every 3 months for a year. The clinic's multidisciplinary PANS team consists of a child and adolescent psychiatrist, a nurse, and 2 clinical psychologists, collaborating with the institute's pediatric neuroinflammation team. The collaboration has resulted in Sweden's first clinical routines for assessment and management of PANS.

In its first 3.5 years, the clinic received 100 referrals for suspected PANS; 47 patients met the diagnostic criteria and 45 consented to participate in research. Twenty-five patients, 56%, were boys, the mean age at symptom onset was 7.5 years, and the mean age at referral to the clinic was 9 years. Nearly all patients (93%) met the standard criteria of acute symptom onset (<72 hours) with temporal relationship to an infection. In the rest, delayed referral prevented a firm attribution, but an infection preceding symptom onset was strongly suspected. Seven patients had onset of an autoimmune or inflammatory disease before symptom onset; these included autoimmune thyroiditis, celiac disease, and type 1 diabetes.

PANS is typically represented as a condition striking previously healthy children. However, preexisting psychiatric illnesses affected nearly 20% of the present cohort. These children had a sudden and severe worsening of symptoms and development of a wider symptom spectrum, and many presented with lab abnormalities. (See table.) Patients in the cohort often received long-term antibiotics, NSAIDs, or intravenous immune globulin without having a systematic assessment of their suspected PANS symptoms. The majority of patients (64%) also had first-, second- or third-degree relatives with ≥1 psychiatric diagnosis, and 76% had an autoimmune disease or inflammatory disorder—most commonly thyroid disease or rheumatoid arthritis. Lab findings suggest that at least some children with PANS had immune dysregulation, but the relationship of these markers to PANS prognosis requires further investigation.

Preexisting Diagnoses, Presenting Psychiatric Symptoms, and Lab Abnormalities	
Preexisting conditions	
Developmental abnormalities	18%
Psychiatric/neuropsychiatric diagnoses	18%
Autoimmune or inflammatory illness	24%
Presenting symptoms affecting ≥50%	
OCD	89%
Anxiety	78%
Emotional lability	71%
Sleep disorder	69%
Attention deficit	63%
Tics	62%
Motor abnormalities	60%
Sensory abnormalities	50%
Deterioration in school	50%
Lab abnormalities	
Positive strep culture	50%
Complement activation	37%
Leukopenia	20%
Positive antinuclear antibodies	17%
Elevated thyroid antibodies	11%

Although the present findings are preliminary, they add to the sparse available evidence characterizing patients with PANS. Long-term follow-up of this cohort is ongoing in an effort to clarify whether any of the common clinical or laboratory findings are

useful in determining if antibiotic, anti-inflammatory, or immunomodulatory treatments should be considered.

Gromark C, Harris R, Wickstrom R, Horne A, et al: Establishing a pediatric acute-onset neuropsychiatric syndrome clinic: baseline clinical features of the pediatric acute-onset neuropsychiatric syndrome cohort at Karolinska Institutet. *Journal of Child and Adolescent Psychopharmacology* 2019 doi 10.1089/cap.2018.0127. From the Karolinska Institutet, Stockholm, Sweden; and other institutions. **Funded by the Stockholm County Council; and other sources. The authors declared no competing interests.**

Optimizing Telepsychiatry for Depression

Telepsychiatry is becoming an accepted venue for treating depression in children and adolescents. Because they are already using video technology to socialize and play, telepsychiatry may be a good treatment fit for most young people. Optimizing the telepsychiatry experience requires attention to legal issues, privacy, audio and video techniques, session design, patient rapport, and good "webside manners."

Telepsychiatry can be defined as the use of Health Insurance Portability and Accountability Act (HIPAA)-compliant videoconferencing. Telepsychiatry can occur in live sessions (synchronous) or with delays (asynchronous). Medications can be prescribed and the patient can be monitored in collaboration with a clinician at the patient's site or the patient's primary care physician. Neuropsychiatric assessments of adverse drug effects, such as the Abnormal Involuntary Movement Scale (AIMS), can be administered over videoconferencing. Prescription of medications for comorbid conditions, including stimulants and benzodiazepines, must be in compliance with federal regulations for prescribing Schedule II controlled substances, including ≥1 in-person visit with the patient. Registration with the Drug Enforcement Administration is also required. A special registration for telepsychiatry was introduced in 2018, with some exceptions to the in-person visit requirement. Several states have additional regulations on telepsychiatry, which clinicians should check regularly.

In order for telepsychiatry sessions to be successful, clinicians may need to adjust how they communicate with patients. Good webside manners require attention to body posture, gestures, eye contact, and tone of voice, keeping in mind the special requirements of being on screen. Because of time delays, verbal encouragement is harder to use in telepsychiatry. Nodding and smiling are important nonverbal strategies to build rapport. If electronic medical records (EMRs) are referenced during a session, they should be placed on the screen below the patient's image so that when glancing at the EMR, the clinician appears to be nodding up and down in a yes-like fashion. Placing the EMR beside the patient image causes negative head shaking gestures. The treatment room should be located near the wifi router to minimize disruptions in the connection. Room selection should optimize comfort, communication, and privacy. Seating, lighting, and audio quality require attention. Commercial telepsychiatry vendors advertise whether their products meet HIPAA-standards, while popular programs like FaceTime are not HIPAA-compliant. Both sites, the provider's and the patient's, must restrict physical access to the session. Audio privacy can be improved using white noise generators, physical barriers, carpeting and other soundproofing elements, or by wearing a headset. The objective is to meet the same HIPAA standards as any clinical site: the patient's and provider's voices should be difficult or impossible to hear outside the videoconferencing room.

Additional information on optimizing the telepsychiatry experience can be found at www.telepsychiatryguide.org. Information on legal regulations can be obtained from the Congressional Research Service (for Schedule II registration) and telemedicine websites such as the American Telemedicine Association (www.americantelmed.org).

Roth D, Ramtekkar U, Zekovic-Roth S: Telepsychiatry: a new treatment venue for pediatric depression. *Child and Adolescent Psychiatry Clinics of North America* 2019;28:377–395. doi 10.1016/j.chc.2019.02.007. From Mind & Body Works, Inc., Honolulu, HI; and Nationwide Children's Hospital, Columbus, OH. **The authors declared no competing interests.**

Suicide, Other Adverse Outcomes of Gabapentinoids

Gabapentinoids were associated with increased risk of suicidal behavior, unintentional opioid overdose, and other adverse behavioral outcomes in a large population-based cohort study. Risk was particularly elevated in the youngest age cohort (i.e., aged 15–24 years). Separate analyses found risk of harm was increased with pregabalin, but not with gabapentin.

Methods: Study data were collected from Swedish national registers and included patients aged ≥15 years who filled ≥2 consecutive prescriptions for gabapentinoids between 2006 and 2013. Study outcomes were compared between periods of gabapentinoid use and nonuse within the same individual.

Results: The cohort consisted of nearly 192,000 individuals who were dispensed pregabalin (>120,000), gabapentin (>85,000), or both (>14,000). Two-thirds of patients were women, and most were aged ≥45 years. In the overall group, 5.2% were treated for suicidal behavior or committed suicide, 8.9% overdosed unintentionally, 6.3% had a road traffic accident or arrest, and 36.7% had a head or body injury. Rates of all of these outcomes were significantly elevated during periods of gabapentinoid use. However, when the 2 drugs were examined separately, risk of most outcomes was elevated only with pregabalin.

Examining gabapentinoids overall, risks for all adverse outcomes were increased significantly in individuals aged 15–24 years (see table) and, to a lesser but still significant extent, in the 25-to-34 age group. Risks were generally lower or not elevated at all in an analysis that excluded persons with substance use disorders. Compared with low to moderate doses, higher doses of gabapentinoids were associated with increased risk of all outcomes.

Associations Between Gabapentinoid Treatment and Adverse Outcomes in Patients Aged 15–24 Years

Outcome	Hazard Ratio*
Suicidal behavior/suicide	1.67
Unintentional overdose	2.4
Head/body injuries	2.08
Traffic incidents	1.4

Discussion: Although gabapentinoids are not approved for psychiatric indications, off-label prescribing is common—up to 90% of the time for pregabalin—often for treatment of alcohol use disorder, generalized anxiety disorder, or social anxiety disorder. While they appear to be safe for a range of behavioral outcomes in older people, more research is needed to clarify the effects of gabapentinoid use in young people.

Molero Y, Larsson H, D'Onofrio B,Sharp D, et al: Associations between gabapentinoids and suicidal behavior, unintentional overdoses, injuries, road traffic incidents, and violent crime: population-based cohort study in Sweden. *BMJ* 2019; doi 10.1136/bmj.l2147. From University of Oxford, UK; and other institutions. **Funded by the Wellcome Trust; and other sources. The authors declared no competing interests.**

Common Drug Trade Names: **gabapentin—*Neurontin*; pregabalin—*Lyrica***

***See Reference Guide.**

Feedback Informed Treatment in Autism

In a randomized trial, feedback informed treatment (FIT), added to usual care, improved quality of life in children with autism spectrum disorder but did not reduce symptom severity.

Methods: Study participants were aged 6–18 years and were referred to any of 8 Dutch multidisciplinary autism care teams. In addition to providing care as usual, the teams were randomly assigned to provide added FIT, and all children treated at a facility were allocated to the treatment provided by their facility. The FIT intervention was a manualized routine in which the therapist administered a questionnaire at the beginning of each session. Children and their

parents, if present, rated the child's well-being on multiple levels, and scores were shown on a graph comparing them with average successful and unsuccessful outcomes in other children. A different questionnaire was administered at the end of each encounter in which the session itself was rated and the result shown on a graph reflecting changes in the way the child was experiencing treatment. Usual treatment included psychoeducation, social skills training, emotion or behavior regulation training, and other therapies. Parent-rated quality of life, measured using the Kidscreen 27 Questionnaire, was the primary efficacy measure. The secondary outcome was change in symptom severity level, evaluated with the Youth Outcome Questionnaire—a non-autism specific parent-rated measure of change in functioning.

Results: A total of 80 children received usual treatment and 86 received FIT. Within the FIT group, 41 received 3–8 sessions of added FIT and 45 received ≥9 FIT sessions. Mean baseline quality of life scores were 96, 92, and 93 in the care as usual, FIT 3–8, and FIT ≥9 groups, respectively. Scores improved in all groups to means of 97–101 points. Overall, gains were larger in children who received FIT, but the difference from usual care was only significant in children who received 3–8 sessions of FIT ($p<0.05$). Of the 5 dimensions on the quality of life questionnaire, FIT in 3–8 sessions was associated with significant improvement in 2: school environment and physical well-being. Participants in all groups demonstrated significant improvement in symptom severity ($p<0.001$), but the addition of FIT was not associated with greater improvement overall. However, children who received FIT did show greater improvement on the hyperactivity and concentration problems ($p=0.049$) and depression and fear ($p=0.054$) subscales.

Discussion: FIT interventions have been evaluated in adults with relatively mild health concerns but have received little study in persons with more severe problems and in children. The present findings suggest it may improve quality of life in children with autism, without significantly improving function. However, it should be noted that the effects of FIT on core symptoms of autism were not evaluated, and whether therapists used the feedback to modify treatment was also not assessed. The finding of little effect for ≥9 sessions of FIT was unexpected and may reflect the nonlinear course of improvement in this disorder. The authors suggest that FIT may bring about positive changes in parents' expectations of therapeutic benefit by fostering supportive interactions with therapists and enhancing a positive view of the child's quality of life.

Study Rating*—15 (89%): This study met most criteria for a randomized controlled trial. However, the use of parent-rated measures prevented blinded outcome evaluations.

de Jong R, Snoek H, Staal W, Klip H: The effect of patients' feedback on treatment outcome in a child and adolescent psychiatric sample: a randomized controlled trial. *European Child & Adolescent Psychiatry* 2019;28:819–834. doi 10.1007/s00787-018-1247-4. From Karakter Child and Adolescent Psychiatry, the Netherlands; and other institutions.
Funded by Karakter Child and Adolescent Psychiatry Centre. The authors declared no competing interests.

***See Reference Guide.**

Adjunctive Folate in Resistant Depression

Outcomes in a series of 10 patients with treatment-resistant depression and documented genetic mutations altering folate metabolism, suggest folate supplement may be moderately effective at improving depressive symptoms.

Background: In adults, low folate levels are associated with a reduced response to antidepressants, and several studies have examined using adjunctive L-methylfolate. There is no prior evidence supporting its use in children or adolescents. L-methylfolate is the metabolically active form of folate, converted from dietary sources by the enzyme methylene tetrahydrofolate reductase (MTHFR). Genetic mutations that affect the function of this enzyme are fairly common and reduce the amount of available L-methylfolate. The only form of folate believed to cross the

blood–brain barrier, L-methylfolate helps to increase monoamine synthesis. L-methylfolate is available as a medical food (*Deplin*), and other forms of folate are available as OTC supplements.

Methods: Subjects were 10 patients, aged 9–17 years (mean age, 14 years; 8 girls) consecutively treated with adjunctive L-methylfolate for resistant depression. All patients underwent genetic testing and showed reduced activity of MTHFR. Patients had an average of 3 comorbid psychiatric diagnoses. The addition of L-methylfolate was considered after ≥2 failed antidepressant trials, and 6 patients were receiving SSRI monotherapy when they started L-methylfolate and 3 were also receiving concomitant second-generation antipsychotic. Changes to patients' antidepressant regimens were not prohibited. L-methylfolate dosing was based on available capsule sizes of *Deplin* (7.5 and 15 mg) and averaged about 9 mg/day. As this was not a controlled study, some families also purchased folate supplements, resulting in significant dose variation, and treatment durations were not standardized (average duration, 38 weeks; range, 16–73 weeks). Efficacy was assessed retrospectively using subjective reports from patients, families, and providers.

Results: Of the 10 patients, 8 reported some improvement, with reductions in symptoms of depression, anxiety, and irritability. Improvement was usually evident within 1 or 2 months. The remaining 2 patients, both with severe depression, experienced no improvement. L-methylfolate was generally well tolerated. A single patient experienced gastrointestinal discomfort that improved with a dose decrease. Another patient experienced worsened anxiety and jitteriness that resolved with a temporary discontinuation and later resuming at a lower dose. These effects could also have been related to antidepressant changes.

Discussion: At present there are no specific guidelines recommending genetic tests for MTHFR activity. Further research is needed to determine when patients with refractory depression should be tested, how the results should be interpreted, and specific products that should be recommended. Although *Deplin* is available as a prescription medical food, it is not covered by most insurance companies, which lead families to turn to OTC products.

Strong conclusions regarding the efficacy of L-methylfolate in resistant depression are not possible based on this research as it was not possible to control for confounding variables, psychotropic medication changes, and product variability. However, the positive results in the small sample of patients suggests that standardized trials may be warranted.

Dartois L, Stutzman D, Morrow M: L-methylfolate augmentation to antidepressants for adolescents with treatment-resistant depression: a case series. *Journal of Child and Adolescent Psychopharmacology* 2019;29:386-391. doi 10.1089/cap.2019.0006. From Seattle Children's Hospital, WA; and children's Hospital Colorado Pediatric Mental Health Institute, Aurora. **Source of funding not stated. The authors declared no competing interests.**

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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.