APA Guidelines for Pediatric Panic Disorder

The recent update to the American Psychiatric Association Practice Guideline for Panic Disorder included a brief overview of the limited data regarding treatment of pediatric panic. Expert opinion supports use of CBT in pediatric panic disorder, but developmental issues will need to be addressed when the program is designed. Although no controlled trials have been conducted, pharmacotherapy also appears to be an acceptable option. An open-label study found SSRIs, alone or in combination with a benzodiazepine, significantly improved panic disorder in 75% of treated adolescents. A chart review of 18 patients aged 7–16 years showed paroxetine significantly reduced panic in 80% of patients and was well tolerated. These studies in combination with randomized controlled trials in other pediatric anxiety disorders suggest SSRIs are a reasonable treatment option. Two case reports and a case series suggest imipramine, alprazolam, and clonazepam may be useful in pediatric panic disorder, but should not be first-line treatment. For a detailed discussion of treatment options see also the American Academy of Child and Adolescent Psychiatry’s Practice Parameter for the Assessment and Treatment of Children and Adolescents With Anxiety Disorders.


Drug Trade Names: alprazolam—Xanax; clonazepam—Klonopin; imipramine—Tofranil; paroxetine—Paxil

Substance Abuse, Depression, and HPA Activity

The combination of high levels of hypothalamic-pituitary-adrenal (HPA) activity and stressful events appears to increase a patient’s vulnerability to substance abuse.

Methods: A group of adolescents (mean age, 15 years) followed for up to 5 years included 55 with depression, 48 at risk of depression based on family history, and 48 comparison subjects.
with no psychiatric risk or diagnosis. Urinary cortisol was measured at baseline as a marker for HPA activity, and annual interviews evaluated and rated the severity of specific stressful life events and the development of a DSM-IV substance abuse disorder. Substance abuse was compared in groups stratified by HPA activity and stressful events.

**Results:** Substance abuse disorders developed in 33 of the 140 participants (24%) and were most prevalent in patients with depression (37%), compared with those at risk (23%) and healthy controls (9%). Urinary cortisol levels had a similar pattern, with the highest values in patients with depression, followed by those at risk and then healthy controls. Substance abuse was more prevalent among patients with high stress and high HPA activity, and it developed in 80% of those with high HPA activity and high stress who had baseline depression and in 50% of those with high levels of both but no baseline depression. Substance abuse developed in 4–19% of those with low stress and low HPA activity.

**Discussion:** The increase in substance abuse among patients with high levels of HPA activity and stressful events appears to be independent of depression which is itself associated with increased risk. Identifying patients with the triad of risk factors (i.e., high stress, high HPA activity, depression) could improve outcomes by allowing for better targeted treatment.

Rao U, Hammen C, Poland R: Mechanisms underlying the comorbidity between depressive and addictive disorders in adolescents: interactions between stress and HPA activity. *American Journal of Psychiatry*. Published online February 17, 2009 at www.ajp.psychiatryonline.org; doi 10.1176/appi.ajp.2008.08030412. From the University of Texas Southwestern Medical Center, Dallas; and other institutions. **Funded by the NIH; and NARSAD. The authors disclosed no conflicts of interest.**

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**QT Prolongation with Anorexia Treatment**

Prospective studies of atypical antipsychotics have not been carried out in pediatric anorexia nervosa, and published data on adverse effects in these patients is limited. Risk factors for QT prolongation include female gender, hypokalemia, and cardiac disease. In addition, some psychotropic medications including atypical antipsychotics can prolong the QT interval.

A 15-year-old female with anorexia nervosa and comorbid mood and anxiety disorders was hospitalized for eating disorder treatment. Medications on admission were 20 mg/day fluoxetine and 5 mg/day olanzapine; her body weight was 106 lbs and her body mass index was 18. Electrocardiogram (ECG) showed a corrected QT (QTc) interval of 457 msec (normal, <450 msec). Olanzapine was stopped and the QTc interval normalized. QTc prolongation recurred when olanzapine was restarted for overwhelming anxiety and when it was subsequently replaced with low-dose risperidone. A trial of low-dose quetiapine did not increase the QTc interval and the dosage was titrated to 50 mg/day with no signs of QT abnormality seen on weekly ECGs. The patient’s anxiety improved and she was able to attain a healthy weight and greater mood stability.

In this patient, the QTc increases were temporally associated with changes in antipsychotic treatment. Although it is possible that an interaction of fluoxetine (a CYP450 1A2 and 2D6 inhibitor) with olanzapine and risperidone (substrates of these CYP enzymes) caused the QTc prolongation, the authors judge it to be an unlikely cause.

Given the frequency of risk factors for QT prolongation and the widespread use of psychotropics in patients with anorexia nervosa as well as the potential consequences of QT prolongation (e.g., torsades de pointes), the importance of cardiac monitoring cannot be overemphasized. In the center at which this patient was treated, all patients with eating disorders receive a baseline ECG. Testing is repeated when a medication that can affect the QT interval is added and when dosage adjustments are made. Patients who purge often experience electrolyte
imbalance and ECG is repeated when this occurs. Medications are withheld and ECGs are repeated until normalization in patients found to have a QTc interval of >450 msec and in cases of an increase >60 msec from baseline.

Ritchie B, Norris M: QTc prolongation associated with atypical antipsychotic use in the treatment of adolescent-onset anorexia nervosa. Journal of the Canadian Academy of Child and Adolescent Psychiatry 2009;18 (February):60–63. From Queen’s University, Kingston, Ont., Canada. The authors have no financial relationships or conflicts of interest to disclose.

Drug Trade Names: fluoxetine—Prozac; olanzapine—Zyprexa; quetiapine—Seroquel; risperidone—Risperdal

Migraine Prophylaxis with Topiramate

There are no drugs FDA approved for pediatric migraine prophylaxis. Topiramate (Topamax) has been effective in adults, and the single trial comprising exclusively young patients showed a trend toward reduced migraine days.1 A new study shows 100 mg/day topiramate is effective migraine prophylaxis in adolescents.2

Methods: Participants in the randomized multisite study (n=106) were aged 12–17 years and had a ≥6 month history of migraine. After screening and a washout of previous preventive therapy, participants received either double-blind topiramate (at 50 or 100 mg/day) or placebo for 16 weeks. Acute headache medications were permitted as needed for symptom relief. Patients recorded headaches and medication use.

Results: Migraine frequency was significantly reduced with 100 mg/day topiramate but not with 50 mg/day. Monthly migraine rates decreased from 4 to 1 with 100 mg/day topiramate and from 4 to 2 with 50 mg/day topiramate and placebo. Response, defined as a ≥50% reduction in migraine attacks, was achieved by 83% of patients who received 100 mg/day topiramate, 46% of those who received 50 mg/day, and 45% of those who received placebo. During the last 4 weeks of double-blind treatment, about half of patients who received 100 mg/day topiramate were migraine free.

Reported adverse effects were consistent with adult studies, and upper respiratory tract infection, paresthesia, and anorexia were more common with topiramate than with placebo. Adverse events of particular concern with topiramate (e.g., rash; oligohidrosis; ocular, renal and hepatic events; hyperammonemia; metabolic acidosis) either did not occur or were not clinically important.

Discussion: Topiramate is typically dosed at >100 mg/day for pediatric epilepsy, and the low rate of serious complications may be dose-related. According to these results, topiramate is effective migraine prophylaxis in adolescents at 100 mg/day but not at 50 mg/day.

Study Rating*—16 (94%): This study met criteria for a quality randomized clinical trial with the exception of a discussion of study limitations and potential bias.


2Lewis D, Winner P, Saper J, Ness S: Randomized, double-blind, placebo-controlled study to evaluate the efficacy and safety of topiramate for migraine prevention in pediatric subjects 12 to 17 years of age. Pediatrics 2009;123 (March):924–934. From Eastern Virginia Medical School, Norfolk; and other institutions. Funded by the NIH; and Ortho-McNeil Janssen Scientific Affairs, LLC.

*Reference Guide item.

PTSD Treatments Reviewed

A survey of treatment practices in pediatric PTSD found the treatment most often prescribed by psychiatrists was pharmacotherapy (20%); other clinicians preferred CBT (23%).1 A systematic review was undertaken to evaluate the evidence-base for individual and group CBT; play...
therapy; art therapy; psychodynamic psychotherapy; pharmacotherapy; and psychological debriefing. Among the treatment modalities reviewed, the evidence was insufficient to support any treatment except CBT, for which the evidence was strong.²

CBT typically combines exposure, cognitive exploration, stress management, relaxation, and other techniques to replace extreme reactions to reminders of the trauma with more realistic associations. A total of 11 studies were identified with the number of CBT sessions ranging from 2 to 20. Regardless of the type of trauma, CBT decreased shame associated with the trauma, improved trust, and enhanced emotional strength, and also decreased overall psychopathology. No harmful effects of CBT were noted.

Taken together, the survey of preferred treatments and the current review showing that only CBT has evidence-based support suggest that about three-fourths of clinicians treating young patients experiencing psychological effects of trauma are employing therapies that are not proven to be effective.


**Lithium Does Not Improve Severe Mood Dysregulation**

Severe mood dysregulation, characterized by nonepisodic irritability and hyperarousal, is not recognized in the DSM-IV and has been suggested to be a “broad phenotype” of bipolar disorder. Because it can reduce irritability and aggression in young patients and is effective in bipolar disorder, lithium was investigated in a small group of patients with severe mood dysregulation.

**Methods:** Patients aged 7–17 years were recruited, and those likely to meet criteria (see box) were evaluated at the NIMH Division of Intramural Research Programs. Patients judged to have severe mood dysregulation (n=45) were admitted to the child psychiatric unit and weaned off all psychotropic medications. Following a 2-week placebo run-in, patients who continued to meet criteria (n=25) were randomized to 6 weeks of double-blind lithium or placebo. Lithium dosages were based on a therapeutic range of 0.8–1.2 mEq/L. Magnetic resonance spectroscopy studies were performed on admission and at study end to evaluate neurometabolic alterations expected to occur with lithium.

**Results:** There were no significant differences between the lithium and placebo groups on any outcome measure including the Clinical Global Impression-Improvement (CGI-I) scale, the Young Mania Rating Scale, the Children’s Depression Rating Scale, and the Conners’ hyperactivity and conduct subscales. A total of 3 lithium-treated patients and 1 placebo-treated patient achieved a CGI-I rating of improved or better. There were also no significant neurometabolic alterations identified on brain scans in either treated group.

**Discussion:** Although the trial’s results were negative, it did have findings that may direct future treatment of severe mood dysregulation. Of the patients admitted, 45% improved enough during the placebo run-in that they no longer

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**Criteria for severe mood dysregulation**

- Irritability evidenced by markedly increased verbal or physical reactivity to negative stimuli ≥3 times per week
- Presence of anger or sadness (i.e., abnormal mood) for at least half of most days
- At least 3 hyperarousal symptoms (i.e., insomnia, agitation, distractibility, racing thoughts, flight of ideas, pressured speech, intrusiveness)
- Severe impairment in ≥1 setting and at least mild impairment in another
- Onset before age 12 years
- Symptoms present for ≥12 months with no symptom-free intervals of >2 months.
met mood dysregulation criteria. This could reflect the therapeutic effect of admission itself, or it may have been related to removal of the patient from environmental triggers such as parents and family members, school, and peers.

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


*Reference Guide Item.

### Lithium Level and Response

In adults, the recommended therapeutic lithium blood level is between 0.8 and 1.5 mEq/L during acute treatment and between 0.6 and 1 mEq/L for maintenance. These adult recommendations have been applied to children and adolescents for whom dosing is recommended to levels of 0.6–1.2 mEq/L. A recent case suggests it is possible for young patients to respond to treatment at substantially lower serum concentrations.

A 14-year-old male (body weight, 106 lbs) with rapid cycling bipolar affective disorder received outpatient treatment with 5 mg/day olanzapine (*Zyprexa*) and 600 mg/day lithium. Lithium was increased to 900 mg/day after lithium concentrations were 0.2 mEq/L at 1 week and 0.3 mEq/L at 2 weeks. The patient achieved euthymia at this dose and olanzapine was discontinued. Lithium was increased to 1200 mg/day. Two weeks later, the patient was judged to be in remission with a lithium level of 0.36 mEq/L. Laboratory results were confirmed at a second independent lab. Repeat measures yielded lithium levels of 0.29–0.48 mEq/L. Although these levels were well below the recommendations, the patient’s response was good and he had no recurrence during 6 months of follow-up.

Kul M, Gokler B, Kultur S: An adolescent with bipolar disorder responding to a lower lithium concentration at maintenance treatment. *Journal of Child and Adolescent Psychopharmacology* 2009;19 (1):97–98. From Hacettepe University Faculty of Medicine, Ankara; and Gaziantep University Medical Faculty, Gaziantep, Turkey. The authors disclosed no conflicts of interest.

### Zinc, Copper, and the Autism Spectrum

A retrospective review found children with pervasive developmental disorders (PDDs) are likely to have a zinc deficiency with associated high serum copper levels. In a large proportion of children studied, the zinc/copper ratio was lower than that previously determined to be normal.

**Background:** Both zinc and copper have a role in the body’s processing of heavy metals including mercury. The elements have antagonistic effects on each other, and low plasma zinc is almost always associated with increased copper levels. Although evidence does not support an association between mercury exposure via thimerosal-containing vaccines and PDDs, there continues to be concern that mercury exposure may contribute to neurodevelopmental disorders.

**Methods:** Retrospective data on zinc and copper levels were reviewed for 230 children with autistic disorder (n=78), pervasive development disorder—not otherwise specified (PDD-NOS; n=110), or Asperger syndrome (n=42) treated at a pediatric neurodevelopmental service center. The cutoff for low plasma zinc was 66 mcg/dL, and for high serum copper the cutoff was 153 mcg/dL. The zinc/copper ratio considered to be low was 0.7.

**Results:** The zinc/copper ratio was <0.7 in 167 (73%) of the 230 patients. Zinc levels were below the cutoff for normal in 47 children (20%), and 39 children (17%) had copper levels above its
cutoff value. Results were similar in diagnostic subgroups. In children with autistic disorder low zinc and high copper levels were present in 19% and 15% of children, respectively, and the zinc/copper ratio was <0.7 in 72%. In PDD-NOS, 19% of children had low zinc levels and 20% had elevated copper levels, and the zinc/copper ratio was <0.7 in 76% of this group. Finally, in Asperger syndrome, rates were 26% for low zinc, 12% for high copper, and 64% had a zinc/copper ratio of <0.7. There were no gender-based differences in any of the concentrations measured.

Discussion: Autistic disorder, PDD-NOS, and Asperger syndrome have distinct behavioral phenotypes. However, the similarities in zinc and copper levels and the resulting zinc/copper ratio suggest the 3 disorders may share a common etiology and therapeutic interventions that could be related to heavy metal processing.

Faber S, Zinn G, Kern II J, Kingston H: The plasma zinc/serum copper ratio as a biomarker in children with autism spectrum disorders. Biomarkers. Published online March 11, 2009 at www.imformaworld.com; doi 10.1080/135475009027883747. From the Children’s Institute; and Duquesne University, Pittsburgh, Penn. The authors report no commercial support or conflicts of interest.