

Panel Finds Poor Evidence for Autism Diets

VITALS

Major Finding: Children with autism spectrum disorders need careful GI evaluations, but there's no good evidence that they have unique gastrointestinal problems or benefit from restricted diets.

Data Source: Literature review and the consensus of an interdisciplinary expert panel

Disclosures: The Autism Forum convened the panel and provided honoraria to its 14 members. One panel member reported relationships with a number of pharmaceutical companies. Another chairs an academic department that derives revenue from genetic laboratory testing.

BY ROBERT FINN

There's no good evidence that children with autism have unique gastrointestinal disorders, nor is there convincing evidence that gluten-free or casein-free diets help these children, according to an expert panel.

The panel, which was convened by the Autism Forum, reached consensus on 23 statements regarding the evaluation, diagnosis, and treatment of gastrointestinal disorders in children with autism

spectrum disorders (ASDs) (Pediatrics 2010;125:S1-S18).

One key recommendation was that children with ASDs need to be evaluated carefully for GI problems because many such children are nonverbal, and even those who are verbal may have difficulty describing their symptoms, such as abdominal pain.

In particular, the panel noted that children with ASDs often respond to GI symptoms by exhibiting problem behaviors such as agitation, aggression, and sleep disturbances.

The panel included experts in child psychiatry, developmental pediatrics, epidemiology, medical genetics, immunology, nursing, pediatric allergy, pediatric gastroenterology, pediatric pain, pediatric neurology, pediatric nutrition, and psychology. Dr. Timothy Buie of Harvard Medical School, Boston, was the paper's lead author.

The recommendations were based on a literature review, but without a formal meta-analysis.

"Because of the absence, in general, of high-quality clinical research data, evidence-based recommendations are not possible at the present time," the panelists wrote. "However, the panel agreed on a number of statements based on expert opinion that arose from a review of existing evidence. It is acknowledged that, in many areas, evidence is generally confined to case reports, observational or descriptive studies, and poorly controlled or uncontrolled studies."

Among the other conclusions were:

- ▶ Children with ASDs are subject to the same common GI disorders as neurotypical children and should be evaluated thoroughly. In particular, clinicians should be sure that these children receive a complete medical evaluation for GI disorders when they present with problem behaviors. Behavioral treatment may complement medical treatment in children with both ASDs and GI disorders, but behavioral treatment alone is not enough.

- ▶ The existence of "autistic enterocolitis" or other gastrointestinal disturbances unique to children with ASDs has not been established, and the evidence for abnormal gastrointestinal permeability ("leaky gut") is limited. More research is needed in these areas, the panel said.

- ▶ Pediatricians and other primary care providers should be alert to nutritional problems in children with ASDs. Some of these children have narrow food preferences, and some parents may put their children on highly restrictive diets that are intended to be therapeutic but result in malnutrition.

In particular, pediatricians should evaluate the child's anthropometry, looking for evidence of wasting, stunting, or changes in growth rate. Children with ASDs should also be evaluated for food intolerance and food allergy, although there is no compelling evidence that these disorders are more prevalent in children with ASDs than in neurotypical children, the panelists reported. ■

occurred in 2% of GEODON patients and at a greater incidence than in placebo. Schizophrenia: *Body as a Whole*—asthenia, accidental injury, chest pain. *Cardiovascular*—tachycardia. *Digestive*—nausea, constipation, dyspepsia, diarrhea, dry mouth, anorexia. *Nervous*—extrapyramidal symptoms, somnolence, akathisia, dizziness. *Respiratory*—respiratory tract infection, rhinitis, cough increased. *Skin and Appendages*—rash, fungal dermatitis. *Special Senses*—abnormal vision. Bipolar Mania: *Body as a Whole*—headache, asthenia, accidental injury. *Cardiovascular*—hypertension. *Digestive*—nausea, diarrhea, dry mouth, vomiting, increased salivation, tongue edema, dysphagia. *Musculoskeletal*—myalgia. *Nervous*—somnolence, extrapyramidal symptoms, dizziness, akathisia, anxiety, hypesthesia, speech disorder. *Respiratory*—pharyngitis, dyspnea. *Skin and Appendages*—fungal dermatitis. *Special Senses*—abnormal vision. **Dose Dependency** An analysis for dose response in the schizophrenia 4-study pool revealed an apparent relation of adverse reaction to dose for the following reactions: asthenia, postural hypotension, anorexia, dry mouth, increased salivation, arthralgia, anxiety, dizziness, dystonia, hypertonia, somnolence, tremor, rhinitis, rash, and abnormal vision. **Extrapyramidal Symptoms (EPS)** The incidence of reported EPS for ziprasidone patients in the short-term, placebo-controlled schizophrenia trials was 14% vs. 8% for placebo. Objectively collected data from those trials on the Simpson-Angus Rating Scale (for EPS) and the Barnes Akathisia Scale (for akathisia) did not generally show a difference between ziprasidone and placebo. **Dystonia** Symptoms of dystonia, prolonged abnormal contractions of muscle groups, may occur in susceptible individuals during the first few days of treatment. While these symptoms can occur at low doses, they occur more frequently and with greater severity with high potency and at higher doses of first generation antipsychotic drugs. Elevated risk of acute dystonia is observed in males and younger age groups. **Vital Sign Changes** Ziprasidone is associated with orthostatic hypotension (see **PRECAUTIONS**). **Weight Gain** In short-term schizophrenia trials, the proportions of patients meeting a weight gain criterion of $\geq 7\%$ of body weight were compared, revealing a statistically significantly greater incidence of weight gain for ziprasidone (10%) compared to placebo (4%). A median weight gain of 0.5 kg was observed in ziprasidone patients compared to no median weight change in placebo patients. Weight gain was reported as an adverse event in 0.4% of both ziprasidone and placebo patients. During long-term therapy with ziprasidone, a categorization of patients at baseline on the basis of body mass index (BMI) revealed the greatest mean weight gain and highest incidence of clinically significant weight gain ($>7\%$ of body weight) in patients with low BMI (<23) compared to normal (23-27) or overweight patients (>27). There was a mean weight gain of 1.4 kg for those patients with a "low" baseline BMI, no mean change for patients with a "normal" BMI, and a 1.3 kg mean weight loss for patients who entered the program with a "high" BMI. **ECG Changes** Ziprasidone is associated with an increase in the QTc interval (see **WARNINGS**). In the schizophrenia trials, ziprasidone was associated with a mean increase in heart rate of 1.4 beats per minute compared to a 0.2 beats per minute decrease among placebo patients. **Other Adverse Events Observed During the Premarketing Evaluation of Ziprasidone in Schizophrenia** Frequent adverse events are those occurring in at least 1/100 patients; infrequent adverse events are those occurring in 1/100 to 1/1000 patients; rare adverse events are those occurring in fewer than 1/1000 patients. *Body as a Whole*—Frequent: abdominal pain, flu syndrome, fever, accidental fall, face edema, chills, photosensitivity reaction, flank pain, hypothermia, motor vehicle accident. *Cardiovascular System*—Frequent: tachycardia, hypertension, postural hypotension. Infrequent: bradycardia, angina pectoris, atrial fibrillation. Rare: first degree AV block, bundle branch block, phlebitis, pulmonary embolus, cardiomegaly, cerebral infarct, cerebrovascular accident, deep thrombophlebitis, myocarditis, thrombophlebitis. *Digestive System*—Frequent: anorexia, vomiting. Infrequent: rectal hemorrhage, dysphagia, tongue edema. Rare: gum hemorrhage, jaundice, fecal impaction, gamma glutamyl trans-peptidase increased, hematemesis, cholestatic jaundice, hepatitis, hepatomegaly, leukoplakia of mouth, fatty liver deposit, melena. *Endocrine*—Rare: hypothyroidism, hyperthyroidism, thyroiditis. *Hemic and Lymphatic System*—Infrequent: anemia, ecchymosis, leukocytosis, leukopenia, eosinophilia, lymphadenopathy. Rare: thrombocytopenia, hypochromic anemia, lymphocytosis, monocytosis, basophilia, lymphedema, polycythemia, thrombocythemia. *Metabolic and Nutritional Disorders*—Infrequent: thirst, transaminase increased, peripheral edema, hyperglycemia, creatine phosphokinase

increased, alkaline phosphatase increased, hypercholesteremia, dehydration, lactic dehydrogenase increased, albuminuria, hypokalemia. Rare: BUN increased, creatinine increased, hyperlipemia, hypocholesteremia, hyperkalemia, hypochloremia, hypoglycemia, hyponatremia, hypoproteinemia, glucose tolerance decreased, gout, hyperchloremia, hyperuricemia, hypocalcemia, hypoglycemic reaction, hypomagnesemia, ketosis, respiratory alkalosis. *Musculoskeletal System*—Frequent: myalgia. Infrequent: tenosynovitis. Rare: myopathy. *Nervous System*—Frequent: agitation, extrapyramidal syndrome, tremor, dystonia, hypertonia, dyskinesia, hostility, twitching, paresthesia, confusion, vertigo, hypokinesia, hyperkinesia, abnormal gait, oculogyric crisis, hypesthesia, ataxia, amnesia, cogwheel rigidity, delirium, hypotonia, akinesia, dysarthria, withdrawal syndrome, buccoglossal syndrome, choreoathetosis, diplopia, incoordination, neuropathy. Infrequent: paralysis. Rare: myoclonus, nystagmus, torticollis, circumoral paresthesia, opisthotonos, reflexes increased, trismus. *Respiratory System*—Frequent: dyspnea. Infrequent: pneumonia, epistaxis. Rare: hemoptysis, laryngismus. *Skin and Appendages*—Infrequent: maculopapular rash, urticaria, alopecia, eczema, exfoliative dermatitis, contact dermatitis, vesiculobullous rash. *Special Senses*—Frequent: fungal dermatitis. Infrequent: conjunctivitis, dry eyes, tinnitus, blepharitis, cataract, photophobia. Rare: eye hemorrhage, visual field defect, keratitis, keratoconjunctivitis. *Urogenital System*—Infrequent: impotence, abnormal ejaculation, amenorrhea, hematuria, menorrhagia, female lactation, polyuria, urinary retention, metrorrhagia, male sexual dysfunction, anorgasmia, glycosuria. Rare: gynecomastia, vaginal hemorrhage, nocturia, oliguria, female sexual dysfunction, uterine hemorrhage. **Adverse Findings Observed in Trials of Intramuscular Ziprasidone** In these studies, the most commonly observed adverse reactions associated with the use of intramuscular ziprasidone ($\geq 5\%$) and observed at a rate on intramuscular ziprasidone (in the higher dose groups) at least twice that of the lowest intramuscular ziprasidone group were headache (13%), nausea (12%), and somnolence (20%). **Adverse Events at an Incidence of $\geq 1\%$ in Short-Term Fixed-Dose Intramuscular Trials** The following list enumerates the treatment-emergent adverse events that occurred in $\geq 1\%$ of patients during acute therapy with intramuscular ziprasidone: *Body as a Whole*—headache, injection site pain, asthenia, abdominal pain, flu syndrome, back pain. *Cardiovascular*—postural hypotension, hypertension, bradycardia, vasodilation. *Digestive*—nausea, rectal hemorrhage, diarrhea, vomiting, dyspepsia, anorexia, constipation, tooth disorder, dry mouth. *Nervous*—dizziness, anxiety, insomnia, somnolence, akathisia, agitation, extrapyramidal syndrome, hypertonia, cogwheel rigidity, paresthesia, personality disorder, psychosis, speech disorder. *Respiratory*—rhinitis. *Skin and Appendages*—furunculosis, sweating. *Urogenital*—dysmenorrhea, priapism. **Other Events Observed During Post-marketing Use** Adverse reaction reports not listed above that have been received since market introduction include rare occurrences of the following—*Cardiac Disorders*: Tachycardia, torsade de pointes (in the presence of multiple confounding factors), (see **WARNINGS**); *Digestive System Disorders*: Swollen Tongue; *Reproductive System and Breast Disorders*: Galactorrhea, priapism; *Nervous System Disorders*: Facial Droop, neuroleptic malignant syndrome, serotonin syndrome (alone or in combination with serotonergic medicinal products), tardive dyskinesia; *Psychiatric Disorders*: Insomnia, mania/hypomania; *Skin and subcutaneous Tissue Disorders*: Allergic reaction (such as allergic dermatitis, angioedema, orofacial edema, urticaria), rash; *Urogenital System Disorders*: Enuresis, urinary incontinence; *Vascular Disorders*: Postural hypotension, syncope.

DRUG ABUSE AND DEPENDENCE

Controlled Substance Class Ziprasidone is not a controlled substance.

OVERDOSAGE

In premarketing trials in over 5400 patients, accidental or intentional overdosage of oral ziprasidone was documented in 10 patients. All patients survived without sequelae. In the patient taking the largest confirmed amount (3240 mg), the only symptoms reported were minimal sedation, slurring of speech, and transitory hypertension (200/95).

