Biomedical Update:

Seroquel: no benefits seen, serious side effects reported in trial

Quetiapine fumarate (Seroquel) is a relatively new antipsychotic drug that resembles the drug clozapine but reportedly is less likely to cause seizures. While the drug appears to be useful in treating schizophrenic adults, a new study indicates that it is of little or no value for autistic children.

Andrés Martin and colleagues conducted a 16-week, open-label trial of the drug, administering it to six autistic male children in dosages ranging from 100 to 350 mg per day. The subjects ranged in age from 6 to 15.

"Overall," Martin et al. report, "there was no statistically significant improvement between baseline and endpoint for the group as a whole." Only two children showed clear benefits from the drug, and these benefits were temporary in one case. The other four subjects had to drop out of the study early, due to side effects including sedation, akathisia (extreme restlessness), increased appetite, weight gain, and, in one case, a seizure.

The researchers conclude that "quetiapine was poorly tolerated and associated with serious side effects" in the group they studied. They note that the small percentage of children responding well to the drug was particularly discouraging in light of the fact that none of the study subjects had histories of being refractory to drug treatment.

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"Open-label quetiapine in the treatment of children and adolescents with autistic disorder," Andrés Martin, Kathleen Koenig, Lawrence Scahill, and Joel Bregman, *Journal of Child and Adolescent Psychopharmacology*, Vol. 9, No. 2, 1999, pp. 99-107. Address: Andrés Martin, Yale Child Study Center, 230 South Frontage Road, P.O. Box 207900, New Haven, CT 06520-7900.

MRS study implicates impaired energy metabolism in autism

Researchers in Michigan report evidence of impaired energy metabolism in autistic children, and suggest that nutritional therapies may help compensate for the abnormality.

Diane Chugani and colleagues, noting that both immunological abnormalities and abnormal serotonin levels are linked to autism, speculated that the amino acid tryptophan may be a key factor in both processes. They note that immune system stress or infection can result in decreased plasma tryptophan, and say, "Tryptophan depletion... may represent an immune mechanism involved in the pathophysiology of autism, or may represent a mechanism of exacerbation of autistic symptoms during immunological stress." In addition to lowering serotonin levels in the brain, they say, reduced plasma tryptophan levels could result in decreased production of nicotinamide dinucleotide (NAD) in the liver, which in turn would impair the functioning of the mitochondria—the "energy factories" of the cells.

One side effect of reduced NAD production would be a build-up of lactate in the plasma and brain. To test their theory, Chugani et al. measured brain lactate, using magnetic resonance spectroscopy (MRS), and plasma lactate in autistic children and controls (siblings in the MRS study, and epileptic patients in the plasma tryptophan study). Nine autistic children participated in the MRS portion of the study, and 15 in the plasma lactate evaluation. In addition, the researchers measured levels of N-acetyl-aspartate (NAA), a chemical that is an indicator of neuronal function. Reduced levels of this substance are implicated in several diseases.

The researchers report that lactate was detected in the frontal cortex of one autistic subject, but none of the controls. NAA levels were significantly reduced in the cerebellum of autistic subjects, and plasma lactate levels were markedly higher in autistic subjects than in the epileptic controls.

"These data," Chugani et al. say, "are consistent with altered energy metabolism in some autistic children, perhaps due to decreased NAD production." They suggest, "A possible therapeutic approach to treat a relative lack of NAD might be to supplement with niacin or to use compounds which have been used to improve mitrochondrial function"—among them the nutritional supplement coenzyme Q10.

The researchers add that their finding of lower NAA in the cerebellum in autistic subjects is consistent with other researchers' reports of decreased numbers of cells in some cerebellar regions.

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"Evidence of altered energy metabolism in autistic children," Diane Chugani, Bhavani S. Sundram, Michael Behen, Mei-Li Lee, and Gregory J. Moore, *Progress in Neuro-Psychopharmacology and Biological Psychiatry*, Vol. 23, 1999, pp. 635-641. Address: Diane Chugani, PET Center, Children's Hospital of Michigan, 3901 Beaubien Blvd., Detroit, MI 48301.

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SSRIs and GI bleeding

A new study indicates that selective serotonin reuptake inhibitors (SSRIs), which include fluoxetine (Prozac), fluvoxamine (Luvox), paroxetine (Paxil), and sertraline (Zoloft), may cause gastrointestinal bleeding in a small percentage of people using the drugs.

Francisco José de Abajo et al. compared 1,651 subjects with upper gastrointestinal (GI) bleeding to 10,000 subjects with no history of GI bleeding. They found that three percent of people in the first group were using SSRIs, compared to only one percent in the latter. People who combined SSRIs with nonsteroidal anti-inflammatory drugs had a 15-fold higher risk of GI bleeding than controls. Aspirin also increased the risk, although less significantly.

"With the exception of fluvoxamine," the researchers say, "all selective serotonin reuptake inhibitors were associated with upper gastrointestinal bleeding." However, they calculate that only about one in 1,300 people taking SSRIs is likely to develop GI bleeding as a result.

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"Association between selective serotonin reuptake inhibitors and upper gastrointestinal bleeding: population based case-control study," Francisco José de Abajo, Luis Alberto García Rodríguez, and Dolores Montero, *British Medical Journal*, Vol. 319, October 23, 1999, pp. 1106-1109. Address: Francisco José de Abajo, Agencia Española del Medicamento, Madrid, Spain, fabajo@agemed.es.

Amenorrhea linked to risperidone treatment

The psychotropic drug risperidone (Risperdal) may cause the cessation of menstruation in some females, according to a recent report by doctors in South Korea.

Y. K. Kim and colleagues report that five of the patients they treated with risperidone stopped menstruating and developed elevated serum prolactin levels. In four cases, the women's periods resumed only when the drug was withdrawn. In the fifth case, menstruation resumed when the drug was tapered.

"These findings," the researchers say, "indicate that the occurrence of amenorrhea during risperidone treatment may be related to elevated serum prolactin levels," possibly caused by the dopmine-receptor-blocking effect of the drug.

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"Risperidone and associated amenorrhea: a report of 5 cases," Y. K. Kim, L. Kim, and M. S. Lee, *Journal of Clinical Psychiatry*, Vol. 60, No. 5, May 1999, pp. 315-317. Address: Y. K. Kim, Department of Psychiatry, College of Medicine, Korea University, Seoul, Korea, yongku@kuccnx.korea.ac.kr.