# Biomedical Update:

## Naltrexone studies differ

Is the drug naltrexone useful in treating autism? One new study says no, while another says yes—but only in a subgroup of autistic children.

In double-blind, placebo crossover studies, Dutch researchers tested naltrexone on 32 retarded subjects: seven with autism, another 16 with both autism and self-injurious behavior (SIB), and nine with SIB but not autism. Participants received a single 100 mg dose, followed by doses of 50 mg or 150 mg per day for four weeks.

Sophie Willemsen-Swinkels and colleagues report that "neither single-dose nor long-term naltrexone hydrochloride treatment had any therapeutic effect on the core symptoms of SIB or autism," and that ratings by staff members actually suggested that the placebo was more effective. In addition, they say, two subjects suffered adverse effects from naltrexone: one became tired and nauseated, while the other exhibited "an acute and severe increase in SIB and acting-out behavior" and had to be isolated for several weeks.

The researchers say their findings suggest that "naltrexone has no clinical value for a broad group of mentally retarded subjects with SIB and/or autism." Previous studies that found naltrexone to be beneficial have been flawed, they say, by small sample size or lack of controls.

A study by French and American researchers, however, suggests that naltrexone may help some autistic children. In a double-blind, placebo-controlled study, Manuel Bouvard and colleagues tested the drug on ten autistic children, at a dose of .5 mg/kg/day, and found that "on all measures ... four strong responders showed a marked decline in symptomatology, while the remaining six subjects exhibited only a marginal sustained decline during the course of the trial." The four strong responders showed reductions in hyperactivity and hostility, and showed improvements in sociability, communication, object relations, and attention.

Blood samples taken from the subjects revealed that the strongest responders to naltrexone had elevated levels of serotonin and arginine-vasopressin, and intermediate elevations of C-terminal β-endorphin. "The best clinical responders," they say, "exhibited the clearest normalization of the elevated plasma chemistries, especially in C-terminal β-endorphin and serotonin."

Bouvard et al. say their results suggest that "naltrexone only benefits a subgroup of autistic children, who may be identified by the presence of certain plasma abnormalities."

Researchers have been testing naltrexone for nearly a decade, because the drug blocks the effects of opioids (naturally occurring opium-like substances in the brain). Some researchers theorize that SIB does not produce pain in autistic individuals because excess opioid production produces an "opioid analgesic" state, while other researchers suggest that autistic children injure themselves to produce an opioid "high."

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"Failure of naltrexone hydrochloride to reduce self-injurious and autistic behavior in mentally retarded adults," Sophie H. N. Willemsen-Swinkels, Jan K. Buitelaar, Gerard J. Nijhof, and Herman van Engeland; *Archives of General Psychiatry*, Vol. 52, September 1995, pp. 766-773. Address: Jan Buitelaar, Department of Child Psychiatry, University of Utrecht, P.O. Box 85500, 3508 GA Utrecht, the Netherlands.

—and—

"Low-dose naltrexone effects on plasma chemistries and clinical symptoms in autism: a double-blind, placebo-controlled study," Manuel P. Bouvard, Marion Leboyer, Jean-Marie Launay, Christophe Recasens, Marie-Hélène Plumet, Delphine Waller-Perotte, François Tabuteau, Dominique Bondoux, Michel Dugas, Patrick Lensing, and Jaak Panksepp, *Psychiatry Research*, Vol. 58, 1995, pp. 191-201. Address: Jaak Panksepp, Department of Psychology, Bowling Green State University, Bowling Green, OH 43403.

## New findings about cerebellum's role

Both MRI scans and post-mortem studies have implicated abnormalities of the cerellum as a cause of autism. But why would defects in a brain area believed to control motor functions cause problems in thinking?

New research by Peter L. Strick suggests that the traditional view of the cerebellum as a coordinator of motor movements is far too limited. Using viruses to track brain circuits in monkeys, Strick discovered that the cerebellum sends messages, by way of the thalamus, to some areas of the cerebral cortex that regulate cognitive, not motor, functions.

Strick next plans to investigate the cerebellum's role in attention, to see if cerebellar defects might explain the attentional deficits of autistic individuals.

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"Viral tracers: neuroscientists use viruses to map out pathways in the brain," Kristin Leutwyler, *Scientific American*, March 1996, p. 18. Address not given.

## CDD group forms

Parents of children diagnosed as having "childhood disintegrative disorder," and professionals who treat children with CDD, are encouraged to join a new network whose purposes are to share information about the disorder; to provide support for people dealing with CDD; and to establish a large group of potential study subjects, in order to aid research into the disorder.

Symptoms of CDD include:

—Apparently normal development for at least three years after birth.

—Loss of previously acquired skills in at least two of the following areas: expressive or receptive language, social skills and adaptive behavior, bowel or bladder control, play skills, or motor skills.

—At least two of the following: impaired social interactions, impaired communication, or restricted, repetitive, and stereotyped patterns of behavior, interests, and activities.

For information about the CDD Network, contact Jenny Fairthorne, Box 3050, Broadway P.O., Nedlands, Perth, West Australia 6009, or Madeline Catalano, 1172 Four Mile Road, Alleghany, NY 14706.

## Buspirone for violence?

A new study supports earlier research suggesting that buspirone, an antianxiety medication, may reduce aggression in autistic individuals.

Marc Hillbrand tested buspirone on a 41-year-old autistic patient who had been hospitalized since age 3, largely because of extremely violent behavior. For several years, the researcher says, the man "was placed in four-point restraints nearly continuously" because of his dangerous aggression and self-injury. Treatment with drugs including haloperidol, lorazepam, lithium, and medroxyprogesterone acetate, as well as seizure drugs including carbamazepine, dilantin, and phenobarbital, was ineffective in controlling his behavior.

Adding buspirone to the man's drug regimen (which, at the time, included haloperidol, phenobarbital, phenytoin, and imipramine) resulted in a marked decrease in violent behavior. At a dose of 80 mg per day, Hillbrand reports, "the frequency and severity of aggression and the use of seclusion and restraints decreased dramatically."

Two year follow-up data, Hillbrand says, "reveal that [the patient] continued to engage only in minimal aggressive behavior." Noting that his findings are preliminary, Hillbrand recommends placebo-controlled, double-blind studies of buspirone on severely aggressive individuals. He notes, however, that buspirone already has been shown to reduce aggression in elderly patients, patients with dementia or brain injuries, and developmentally disabled individuals.

Two earlier studies also suggest that buspirone might be useful in treating behavior problems in autistic individuals. In 1991, A. Gedye reported that a female patient's aggression decreased by 67% during buspirone treatment (see ARRI 5/4). And in 1989, George Realmuto et al. tested the drug on four autistic children and reported that the hyperactivity of two children decreased, and that one child exhibited fewer stereotypical behaviors (see ARRI 4/3).

While no side effects were reported in the current studies, buspirone can cause chest pains, heart irregularities, lightheadedness, nausea, restlessness, dizziness, fatigue, dry mouth, and other side effects.

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"The use of buspirone with aggressive behavior" (letter), Marc Hillbrand; *Journal of Autism and Developmental Disorders*, Vol. 25, No. 6, December 1995, pp. 663-664. Address not given.