# Fenfluramine debate continues (from page 1)

More support for the use of fenfluramine came from a study by Gene Stubbs et al., who tested the drug on eight autistic children and reported that their results "confirm our previous findings that fenfluramine can ameliorate symptoms of some patients with the syndrome of autism...[although] that improvement may be limited to the narrow range of patients with initial IQs above 40 and with motor symptoms."

According to the study, teachers reported behavior improvements in three subjects during fenfluramine administration; motor abnormalities decreased significantly in the overall group; and one child's IQ increased from 55 to 69, while another child had an 18-month academic gain over the course of a year.

Stubbs' findings, however, have been sharply criticized by Farber, who states that "the results described (in the study) belie the strongly positive conclusions reached by the paper." He notes that 1) all parents noticed improvement on the placebo, while both negative and positive results were reported during administration of the drug; 2) only one young, high-functioning child had an IQ rise of more than six points, and spontaneous IQ improvement in such autistic children is not uncommon; and 3) "the only statistically significant finding reported in the entire study" was a decrease in abnormal motor behavior.

Magda Campbell and her colleagues administered the drug to ten autistic children and reported that "a variety of positive stimulating and tranquilizing effects of fenfluramine were observed," including increased relatedness and animated facial expression, improved sleep patterns, and decreases in irritability, temper tantrums, aggressiveness, self-mutilation and hyperactivity. Unlike the study by Stubbs et al., this study indicated that children with the *lowest* IQs seemed to benefit most from the drug.

R. de Villard et al., in an open clinical trial of 76 autistic children and 36 normal children with behavior problems, reported generally favorable results when fenfluramine and sometimes methylphenidate (Ritalin) were given. Benefits included increased calmness, better sleep, and more responsiveness. Side effects included diarrhea, cramps, anorexia and crying. Unfortunately, because of mixing of treatments and of types of subjects, and failure to report numbers of cases in any category, this report's findings are difficult to evaluate.

While Stubbs and Edward Geller reported that fenfluramine caused an improvement in IQ scores in some autistic individuals, most studies—even those reporting other positive results—are not in agreement. Studies by Gerald Groden, William Klykylo and Gerald August all reported some improvements in behavior and attention, but none of these researchers found any improvement in IQ scores.

According to one 1987 study, fenfluramine may be a useful treatment for the stereotypical breathing behaviors and resulting fainting spells which occur in some developmentally disabled individuals. Henri Gastault et al. tested fenfluramine's effectiveness in suppressing the breathing stereotypies of eight children—including four autistic or autistic-like children and two girls suspected of having Rett Syndrome—and saw improvement in all but one case.

### Some studies negative

In a study published in the most recent issue of the Journal of Autism and Developmental Disorders, a research team headed by Elsie Yarbrough administered fenfluramine to 20 autistic subjects and found that it "caused no significant reductions in maladaptive behaviors." The researchers also reported that 65% of the subjects exhibited side effects including tension and agitation, insomnia and sweating. "Severe withdrawal effects" were seen in nine subjects.

The researchers conclude that "the lack of any significant positive findings and the presence of adverse side effects strongly indicate the need for caution in the use of fenfluramine with severely disabled, autistic individuals."

A nine-month study of six autistic boys conducted by Jean Madsen Beisler and her associates measured the effectiveness of the drug using formal tests, spontaneous language samples, number of noncommunicative utterances, instances of immediate echolalia, and number of spontaneous initiations; they report that "it is apparent from the data that for nearly every combination of language measurements and observations, there is no consistent pattern of changes that could be attributed to the drug regimen for the group as a whole."

Helena Ho and fellow researchers recently tested the effects of fenfluramine on seven autistic children and reported that there were no significant improvements in IQ scores. Slight improvements were seen in short-term auditory memory and some receptive language skills; however, the researchers questioned the improvement in receptive language, as several children taking a placebo showed similar gains.

A study by Eugene R. Schnitzler et al., involving four autistic children and using a 10-month double-blind placebo crossover design, reported that "no definite clinical improvements were seen."

### Side effects noted

While the debate continues over whether or not fenfluramine is of value in treating autism, there is increasing concern about the side effects of the drug and about the possible risks of long- term administration.

In the Campbell study, the majority of children exhibited drowsiness and "excessive and uncontrollable irritability." A study of 14 children by George Realmuto and his associates indicates that listlessness, food refusal and stomach upsets are common in the early stages of fenfluramine use, while irritability, agitation and crying frequently appear after several months.

Two of the 14 children in the Realmuto study developed grand mal seizures, leading him to state that "further studies are necessary to evaluate the possible increased risk for seizures following fenfluramine use."

Leonard Piggott and fellow researchers studied eight children taking fenfluramine and found that four developed side effects, including drowsiness, lethargy, loss of appetite, irritability, and bowel and bladder problems; these symptoms disappeared when dosages were reduced. One child developed an ulcer while on the drug, but the researchers say this may have been coincidental. In the Schnitzler et al. study, one of the four subjects showed "excessive irritability and aggressive outbursts."

### Is fenfluramine a neurotoxin?

Stubbs' subjects developed a number of unpleasant side effects including skin rashes, sleep disturbances and mood disturbances; but in spite of these problems, he believes that "it is worthwhile to continue research on fenfluramine for autistic patients."

*Animal studies raise serious concerns that fenfluramine may damage brain cells.*

Gualtieri disagrees, warning that "there is some concern that the drug may be neurotoxic"; he believes that "fenfluramine should not be prescribed to autistic children by practitioners under any circumstances, and the drug should be gradually withdrawn from children who are currently receiving it."

Ritvo allows that "there are reports that comparatively high single doses of fenfluramine in the rat produce darkening of cells in the B-9 nucleus in the midbrain, loss of nuclear detail, and cellular shrinkage", as well as long-lasting changes in neurotransmitter metabolism, and says that "this...suggests damage to nerve terminals that could regenerate if damage is not excessive." He notes that rabbits are unaffected by fenfluramine, and that studies on monkeys suggest that effects of the drug are reversible.

Researchers John Harvey and Scott McMaster express concern about the drug's effects; they injected rats with fenfluramine and found that "the neurotoxic actions of fenfluramine...extend beyond the actions on the serotonin cell bodies in the B-9 region," and also affect neurons in the amygdala and hippocampus, areas of the brain's limbic system. They add that the effects occurred even when small doses were administered.

Neurologists Michael Pranzatelli and S. Robert Snodgrass believe animal studies indicate that fenfluramine is a neurotoxin and a "poor agent for human therapeutics"; in addition they note that convulsions and coma have been reported in humans receiving doses as low as five milligrams per kilogram, approximately three times the standard dose used with autistic individuals.

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