Direct Genetic Links to ADHD Identified

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FROM THE LANCET

Attention-deficit/hyperactivity disorder is a neurodevelopmental disorder, rather than a purely social construct, according to British researchers who have found that a type of genetic variation associated with brain disorders such as schizophrenia and autism also occurs in excess in ADHD patients.

The findings, published online, provide the first direct evidence of a genetic basis for ADHD, Dr. Nigel Williams of Cardiff University, Wales, and his colleagues reported (Lancet 2010 [doi: 10.1016/S0140-6736(10)61109-9]).

The investigators performed a genome-wide analysis of large, rare chromosomal deletions and duplications known as copy number variants (CNVs) in 366 children with ADHD and 1,047 controls. The genome-wide burden of CNVs was significantly greater in the ADHD patients, compared with that in the controls – rates of 0.156 and 0.075, respectively, they found.

The CNVs identified in this study are similar to those found in patients with schizophrenia and autism, and are significantly enriched for loci that have previously been implicated in those disorders – with particular overlap at a region on chromosome 16 that spans numerous genes, including one that affects brain development.

Furthermore, although the rate of CNVs was significantly higher in children with ADHD with and without intellectual disability, compared with the general population, the rate was particularly high in those with intellectual disability, defined as those with an IQ of less than 70 (rates of 0.424 and 0.075, respectively).

VITALS

Major Finding: The genome-wide burden of CNVs was significantly greater in the ADHD patients, compared with the controls (rates of 0.156 vs. 0.075, respectively).

Data Source: A genome-wide analysis of CNVs in 366 children with ADHD and 1,047 controls.

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The findings are noteworthy because despite evidence that ADHD might be a genetic condition – for example, it has an estimated heritability of 76% – there has been a great deal of debate over whether it is a result of bad parenting or other external factors, coauthor Dr. Anita Thapar said during a press conference on the findings. "ADHD can be stigmatizing … and finding this direct genetic link to ADHD should help clear this misunderstanding and address this issue of stigma," said Dr. Thapar, professor of child and adolescent psychiatry at Cardiff University.

In addition to providing a window into the biology of the brain, the findings also will influence the way in which ADHD is classified and will improve communication between scientists and clinicians about "what we mean by ADHD," she said.

"This will be the start of a much more scientific venture, because our findings are going to help us unravel the biologic basis of ADHD, and that's going to be really important in turn in the further future to help us develop new and much more effective treatments for affected individuals."

The subjects were aged 5-17 years (mean, 10.5 years), were of white U.K. origin, and had a mean IQ of 86. Controls were unrelated, ethnically matched children from the 1958 British Birth Cohort.

The findings have important implications. "Our results emphasize that further investigation of CNVs in ADHD is a priority for research into this disorder," the investigators wrote. ■

5.15 Potential for Cognitive and Motor Impairment
FANAPT, like other antipsychotics, has the potential to impair judgment, thinking or motor skills. In short-term, placebo-controlled trials, somnolence (including sedation) was reported in 11.9% (104/874) of adult patients treated with FANAPT at doses of 10 mg/day or greater versus 5.3% (31/587) treated with placebo. Patients should be cautioned about operating hazardous machinery, including automobiles, until they are reasonably certain that therapy with FANAPT does not affect them adversely.

6 ADVERSE REACTIONS

6.1 Clinical Studies Experience
Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trial of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in clinical practice. The information below is derived from a clinical trial database for FANAPT consisting of 2070 patients exposed to FANAPT at doses of 10 mg/day or greater, for the treatment of schizophrenia. All of these patients who received FANAPT were participating in multiple-dose clinical trials. The conditions and duration of treatment with FANAPT varied greatly and included (in overlapping categories), open-label and double-blind phases of studies, inpatients and outpatients, fixed-dose and flexible-dose studies, and short-term and longer-term exposure.

Adverse reactions during exposure were obtained by general inquiry and recorded by clinical investigators using their own terminology. Consequently, to provide a meaningful estimate of the proportion of individuals experiencing adverse reactions, reactions were grouped in standardized categories using MedDRA terminology.

The stated frequencies of adverse reactions represent the proportions of individuals who experienced a treatment-emergent adverse reaction of the type listed. A reaction was considered treatment emergent if it occurred for the first time or worsened while receiving therapy following baseline evaluation.

The information presented in these sections was derived from pooled data from four placebo-controlled, 4- or 6-week, fixed- or flexible-dose studies in patients who received FANAPT at daily doses within a range of 10 to 24 mg (n=874).

Adverse Reactions Occurring at an Incidence of 2% or More among FANAPT-Treated Patients and More Frequent than Placebo
Table 1 enumerates the pooled incidences of treatment-emergent adverse reactions that were spontaneously reported in four placebo-controlled, 4- or 6-week, fixed- or flexible-dose studies, listing those reactions that occurred in 2% or more of patients treated with FANAPT in any of the dose groups, and for which the incidence in FANAPT-treated patients in any dose group was greater than the incidence in patients treated with placebo.

Table 1: Treatment-Emergent Adverse Reactions in Short-Term, Fixed- or Flexible-Dose, Placebo-Controlled Trials in Adult Patients*

Body System or Organ Class Dictionary-derived Term	Percentage of Patients Reporting Reaction Placebo (N=587)	 FANAPT 10-16 mg/day (N=483)	 FANAPT 20-24 mg/day (N=391)
Body as a Whole			
Arthralgia	2	3	3
Fatigue	3	4	6
Musculoskeletal Stiffness	1	1	3
Weight Increased	1	1	9
Cardiac Disorders			
Tachycardia	1	3	12
Eye Disorders			
Vision Blurred	2	3	1
Gastrointestinal Disorders			
Nausea	8	7	10
Dry Mouth	1	8	10
Diarrhea	4	5	7
Abdominal Discomfort	1	1	3
Infections			
Nasopharyngitis	3	4	3
Upper Respiratory Tract Infection	1	2	3
Nervous System Disorders			
Dizziness	7	10	20
Somnolence	5	9	15
Extrapyramidal Disorder	4	5	4
Tremor	2	3	3
Lethargy	1	3	1

(continued)

Table 1: Treatment-Emergent Adverse Reactions in Short-Term, Fixed- or Flexible-Dose, Placebo-Controlled Trials in Adult Patients*

Body System or Organ Class Dictionary-derived Term	Percentage of Patients Reporting Reaction Placebo (N=587)	 FANAPT 10-16 mg/day (N=483)	 FANAPT 20-24 mg/day (N=391)
Reproductive System			
Ejaculation Failure	<1	2	2
Respiratory			
Nasal Congestion	2	5	8
Dyspnea	<1	2	2
Skin			
Rash	2	3	2
Vascular Disorders			
Orthostatic Hypotension	1	3	5
Hypotension	<1	<1	3

*Table includes adverse reactions that were reported in 2% or more of patients in any of the FANAPT dose groups and which occurred at greater incidence than in the placebo group. Figures rounded to the nearest integer.

Dose-Related Adverse Reactions in Clinical Trials
Based on the pooled data from four placebo-controlled, 4- or 6-week, fixed- or flexible-dose studies, adverse reactions that occurred with a greater than 2% incidence in the patients treated with FANAPT, and for which the incidence in patients treated with FANAPT 20-24 mg/day were twice than the incidence in patients treated with FANAPT 10-16 mg/day were: abdominal discomfort, dizziness, hypotension, musculoskeletal stiffness, tachycardia, and weight increased.

Common and Drug-Related Adverse Reactions in Clinical Trials
Based on the pooled data from four placebo-controlled, 4- or 6-week, fixed- or flexible-dose studies, the following adverse reactions occurred in ≥5% incidence in the patients treated with FANAPT and at least twice the placebo rate for at least one dose: dizziness, dry mouth, fatigue, nasal congestion, somnolence, tachycardia, orthostatic hypotension, and weight increased. Dizziness, tachycardia, and weight increased were at least twice as common on 20-24 mg/day as on 10-16 mg/day.

Extrapyramidal Symptoms (EPS) in Clinical Trials
Pooled data from the four placebo-controlled, 4- or 6-week, fixed- or flexible-dose studies provided information regarding treatment-emergent EPS. Adverse event data collected from those trials showed the following rates of EPS-related adverse events as shown in Table 2.

Table 2: Percentage of EPS Compared to Placebo

Adverse Event Term	Placebo (%) (N=587)	FANAPT 10-16 mg/day (%) (N=483)	FANAPT 20-24 mg/day (%) (N=391)
All EPS events	**11.6**	**13.5**	**15.1**
Akathisia	2.7	1.7	2.3
Bradykinesia	0	0.6	0.5
Dyskinesia	1.5	1.7	1.0
Dystonia	0.7	1.0	0.8
Parkinsonism	0	0.2	0.3
Tremor	1.9	2.5	3.1

Adverse Reactions Associated with Discontinuation of Treatment in Clinical Trials
Based on the pooled data from four placebo-controlled, 4- or 6-week, fixed- or flexible-dose studies, there was no difference in the incidence of discontinuation due to adverse events between FANAPT-treated (5%) and placebo-treated (5%) patients. The types of adverse events that led to discontinuation were similar for the FANAPT- and placebo-treated patients.

Demographic Differences in Adverse Reactions in Clinical Trials
An examination of population subgroups in the four placebo-controlled, 4- or 6-week, fixed- or flexible-dose studies did not reveal any evidence of differences in safety on the basis of age, gender or race *[see Warnings and Precautions (5.1)]*.

Laboratory Test Abnormalities in Clinical Trials
A between-group comparison of the pooled data from four placebo-controlled, 4- or 6-week studies, revealed no medically important differences between FANAPT and placebo in mean change from baseline to endpoint in routine hematology, urinalysis, or serum chemistry, including glucose. Similarly, there were no medically important changes in triglyceride and total cholesterol measurements (Table 3). There were no differences between FANAPT and placebo in the incidence of discontinuation due to changes in hematology, urinalysis, or serum chemistry.