

# 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).

Given these considerations, FANAPT should be prescribed in a manner that is most likely to minimize the occurrence of tardive dyskinesia. Chronic antipsychotic treatment should generally be reserved for patients who suffer from a chronic illness that (1) is known to respond to antipsychotic drugs, and (2) for whom alternative, equally effective, but potentially less harmful treatments are not available or appropriate. In patients who do require chronic treatment, the smallest dose and the shortest duration of treatment producing a satisfactory clinical response should be sought. The need for continued treatment should be reassessed periodically.

If signs and symptoms of tardive dyskinesia appear in a patient on FANAPT, drug discontinuation should be considered. However, some patients may require treatment with FANAPT despite the presence of the syndrome.

## 5.5 Hyperglycemia and Diabetes Mellitus

Hyperglycemia, in some cases extreme and associated with ketoacidosis or hyperosmolar coma or death, has been reported in patients treated with atypical antipsychotics including FANAPT. Assessment of the relationship between atypical antipsychotic use and glucose abnormalities is complicated by the possibility of an increased background risk of diabetes mellitus in patients with schizophrenia and the increasing incidence of diabetes mellitus in the general population. Given these confounders, the relationship between atypical antipsychotic use and hyperglycemia-related adverse events is not completely understood. However, epidemiological studies suggest an increased risk of treatment-emergent hyperglycemia-related adverse events in patients treated with the atypical antipsychotics included in these studies. Because FANAPT was not marketed at the time these studies were performed, it is not known if FANAPT is associated with this increased risk. Precise risk estimates for hyperglycemia-related adverse events in patients treated with atypical antipsychotics are not available.

Patients with an established diagnosis of diabetes mellitus who are started on atypical antipsychotics should be monitored regularly for worsening of glucose control. Patients with risk factors for diabetes mellitus (e.g., obesity, family history of diabetes) who are starting treatment with atypical antipsychotics should undergo fasting blood glucose testing at the beginning of treatment and periodically during treatment. Any patient treated with atypical antipsychotics should be monitored for symptoms of hyperglycemia including polydipsia, polyuria, polyphagia, and weakness. Patients who develop symptoms of hyperglycemia during treatment with atypical antipsychotics should undergo fasting blood glucose testing. In some cases, hyperglycemia has resolved when the atypical antipsychotic was discontinued; however, some patients required continuation of antidiabetic treatment despite discontinuation of the suspect drug.

## 5.6 Weight Gain

Based on the pooled data from the four placebo-controlled, 4- or 6-week, fixed- or flexible-dose studies, the proportions of patients having a weight gain of  $\geq 7\%$  body weight was 12% for FANAPT 10-16 mg/day, 18% for FANAPT 20-24 mg/day, and 13% for FANAPT (combined doses) versus 4% for placebo. The mean weight change from baseline to endpoint in the short-term studies was -0.1 kg for placebo versus 2.0 kg for FANAPT-treated patients. Across all short- and long-term studies, the overall mean change from baseline at endpoint was 2.1 kg.

## 5.7 Seizures

In short-term placebo-controlled trials (4- to 6-weeks), seizures occurred in 0.1% (1/1344) of patients treated with FANAPT compared to 0.3% (2/587) on placebo. As with other antipsychotics, FANAPT should be used cautiously in patients with a history of seizures or with conditions that potentially lower the seizure threshold, e.g., Alzheimer's dementia. Conditions that lower the seizure threshold may be more prevalent in a population of 65 years or older.

## 5.8 Orthostatic Hypotension and Syncope

FANAPT can induce orthostatic hypotension associated with dizziness, tachycardia, and syncope. This reflects its  $\alpha_1$ -adrenergic antagonist properties. In double-blind placebo-controlled short-term studies, where the dose was increased slowly, as recommended above, syncope was reported in 0.4% (5/1344) of patients treated with FANAPT, compared with 0.2% (1/587) on placebo. Orthostatic hypotension was reported in 5% of patients given 20-24 mg/day, 3% of patients given 10-16 mg/day, and 1% of patients given placebo. More rapid titration would be expected to increase the rate of orthostatic hypotension and syncope.

FANAPT should be used with caution in patients with known cardiovascular disease (e.g., heart failure, history of myocardial infarction, ischemia, or conduction abnormalities), cerebrovascular disease, or conditions that predispose the patient to hypotension (dehydration, hypovolemia, and treatment with antihypertensive medications). Monitoring of orthostatic vital signs should be considered in patients who are vulnerable to hypotension.

## 5.9 Leukopenia, Neutropenia and Agranulocytosis

In clinical trial and postmarketing experience, events of leukopenia/neutropenia have been reported temporally related to antipsychotic agents. Agranulocytosis (including fatal cases) has also been reported.

Possible risk factors for leukopenia/neutropenia include preexisting low white blood cell count (WBC) and history of drug induced leukopenia/neutropenia. Patients with a pre-existing low WBC or a history of drug induced leukopenia/neutropenia should have their complete blood count (CBC) monitored frequently during the first few months of therapy and should discontinue FANAPT at the first sign of a decline in WBC in the absence of other causative factors.

Patients with neutropenia should be carefully monitored for fever or other symptoms or signs of infection and treated promptly if such symptoms or signs occur. Patients with severe neutropenia (absolute neutrophil count  $<1000/\text{mm}^3$ ) should discontinue FANAPT and have their WBC followed until recovery.

## 5.10 Hyperprolactinemia

As with other drugs that antagonize dopamine D2 receptors, FANAPT elevates prolactin levels.

Hyperprolactinemia may suppress hypothalamic GnRH, resulting in reduced pituitary gonadotropin secretion. This, in turn, may inhibit reproductive function by impairing gonadalsteroidogenesis in both female and male patients. Galactorrhea, amenorrhea, gynecomastia, and impotence have been reported with prolactin-elevating compounds. Long-standing hyperprolactinemia when associated with hypogonadism may lead to decreased bone density in both female and male patients.

Tissue culture experiments indicate that approximately one-third of human breast cancers are prolactin-dependent *in vitro*, a factor of potential importance if the prescription of these drugs is contemplated in a patient with previously detected breast cancer. Mammary gland proliferative changes and increases in serum prolactin were seen in mice and rats treated with FANAPT [see *Nonclinical Toxicology (13.1) in the full prescribing information*]. Neither clinical studies nor epidemiologic studies conducted to date have shown an association between chronic administration of this class of drugs and tumorigenesis in humans; the available evidence is considered too limited to be conclusive at this time.

In a short-term placebo-controlled trial (4-weeks), the mean change from baseline to endpoint in plasma prolactin levels for the FANAPT 24 mg/day-treated group was an increase of 2.6 ng/mL compared to a decrease of 6.3 ng/mL in the placebo-group. In this trial, elevated plasma prolactin levels were observed in 26% of adults treated with FANAPT compared to 12% in the placebo group. In the short-term trials, FANAPT was associated with modest levels of prolactin elevation compared to greater prolactin elevations observed with some other antipsychotic agents. In pooled analysis from clinical studies including longer term trials, in 3210 adults treated with iloperidone, gynecomastia was reported in 2 male subjects (0.1%) compared to 0% in placebo-treated patients, and galactorrhea was reported in 8 female subjects (0.2%) compared to 3 female subjects (0.5%) in placebo-treated patients.

## 5.11 Body Temperature Regulation

Disruption of the body's ability to reduce core body temperature has been attributed to antipsychotic agents. Appropriate care is advised when prescribing FANAPT for patients who will be experiencing conditions which may contribute to an elevation in core body temperature, e.g., exercising strenuously, exposure to extreme heat, receiving concomitant medication with anticholinergic activity, or being subject to dehydration.

## 5.12 Dysphagia

Esophageal dysmotility and aspiration have been associated with antipsychotic drug use. Aspiration pneumonia is a common cause of morbidity and mortality in elderly patients, in particular those with advanced Alzheimer's dementia. FANAPT and other antipsychotic drugs should be used cautiously in patients at risk for aspiration pneumonia [see *Boxed Warning*].

## 5.13 Suicide

The possibility of a suicide attempt is inherent in psychotic illness, and close supervision of high-risk patients should accompany drug therapy. Prescriptions for FANAPT should be written for the smallest quantity of tablets consistent with good patient management in order to reduce the risk of overdose.

## 5.14 Priapism

Three cases of priapism were reported in the pre-marketing FANAPT program. Drugs with  $\alpha$ -adrenergic blocking effects have been reported to induce priapism. FANAPT shares this pharmacologic activity. Severe priapism may require surgical intervention.

## 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.

**Disclosures:** The study was funded primarily by Wellcome Trust. Additional funding was provided by Action Research, Baily Thomas Charitable Trust, UK Medical Research Council, and the European Union. Study authors stated that they had no conflicts to report.

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)
<b>Body as a Whole</b>			
Arthralgia	2	3	3
Fatigue	3	4	6
Musculoskeletal Stiffness	1	1	3
Weight Increased	1	1	9
<b>Cardiac Disorders</b>			
Tachycardia	1	3	12
<b>Eye Disorders</b>			
Vision Blurred	2	3	1
<b>Gastrointestinal Disorders</b>			
Nausea	8	7	10
Dry Mouth	1	8	10
Diarrhea	4	5	7
Abdominal Discomfort	1	1	3
<b>Infections</b>			
Nasopharyngitis	3	4	3
Upper Respiratory Tract Infection	1	2	3
<b>Nervous System Disorders</b>			
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)
<b>Reproductive System</b>			
Ejaculation Failure	<1	2	2
<b>Respiratory</b>			
Nasal Congestion	2	5	8
Dyspnea	<1	2	2
<b>Skin</b>			
Rash	2	3	2
<b>Vascular Disorders</b>			
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 (%)	FANAPT 10-16 mg/day (%)	FANAPT 20-24 mg/day (%)
	(N=587)	(N=483)	(N=391)
<b>All EPS events</b>	<b>11.6</b>	<b>13.5</b>	<b>15.1</b>
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.