Immune Dysregulation Seen in Autistic Children

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BUDAPEST, HUNGARY — Children with autism spectrum disorders appear to have immune responses different from those of healthy children, according to data presented at the 4th International Congress on Autoimmunity.

"There is evidence now for an immune dysregulation in children with autism, compared with children in the general population," said Paul Ashwood, Ph.D., of the University of California, Davis.

In a study of 31 children with autism spectrum disorders (ASD) and 19 typically developing control children aged 2-5 years, the children with ASD had abnormal levels of several cytokines in response to stimulation with three antigens, compared with the control children.

The study adds weight to the idea that autism has an immune component. There are several previous reports of both increased autoimmunity and immune response deficits in children with ASD. "However, a lot of these reports are conflicting, and there is no consensus so far," Dr. Ashwood said.

In this study, Dr. Ashwood and colleagues isolated and stimulated peripheral blood mononuclear cells for 48 hours with phytohemagglutinin, lipopolysaccharide, and vaccine antigens from tetanus and MMR. Analysis was performed for 18 cytokines. At baseline, cytokine levels were similar in the children with ASD and the control children.

Following stimulation with phytohemagglutinin, the children with ASD had statistically significantly lower levels of IL-2, IL-6, IL-10, and IL-12 than the control children. There was also a trend toward higher levels of IL-13 and granulocyte macrophage-colony stimulating factor—which stimulates the precursor cells of granulocytes, macrophages, and eosinophils—among the children with ASD than the control children.

A similar pattern was seen after stimulation with lipopolysaccharide. Children with ASD had lower levels of IL-12 and a slight increase in granulocyte macrophage-colony stimulating factor, compared with the control children.

Stimulation with tetanus antigens resulted in lower levels of IFN-γ, IL-1-η, IL-12, and granulocyte macrophage-colony stimulating factor in the children with ASD, compared to the control children.

Although there was no difference after stimulation with MMR vaccine antigens the researchers are planning to investigate the response to individual components of the MMR vaccine. ■

Campral®
(acamprosate calcium)
Delayed-Release Tablets

Rx only

Brief Summary:
For complete details, please see full Prescribing Information for CAMPRAL

INDICATIONS AND USAGE
CAMPRAL (acamprosate calcium) is indicated for the maintenance of abstinence from alcohol in patients with alcohol dependence who are abstinent at treatment initiation. Treatment with CAMPRAL should be part of a comprehensive management program that includes psychosocial support. The efficacy of CAMPRAL in promoting abstinence has not been demonstrated in subjects who have not undergone detoxification and not achieved alcohol abstinence prior to beginning CAMPRAL treatment. The efficacy of CAMPRAL in promoting abstinence from alcohol in polysubstance abusers has not been adequately assessed.

CONTRAINDICATIONS
CAMPRAL is contraindicated in patients who previously have exhibited hypersensitivity to acamprosate calcium or any of its components. CAMPRAL is contraindicated in patients with severe renal impairment (creatinine clearance ≤30 mL/min).

PRECAUTIONS
Use of CAMPRAL does not eliminate or diminish withdrawal symptoms. **General: Renal Impairment** Treatment with CAMPRAL in patients with moderate renal impairment (creatinine clearance of 30-50 mL/min) requires a dose reduction. Patients with severe renal impairment (creatinine clearance of ≤30 mL/min) should not be given CAMPRAL (see also CONTRAINDICATIONS). **Suicidality** In controlled clinical trials of CAMPRAL, adverse events of a suicidal nature (suicidal ideation, suicide attempts, completed suicides) were infrequent overall, but were more common in CAMPRAL-treated patients than in patients treated with placebo (1.4% vs. 0.5% in studies of 6 months or less; 2.4% vs. 0.8% in year-long studies). Completed suicides occurred in 3 of 2272 (0.13%) patients in the pooled acamprosate group from all controlled studies and 2 of 1962 patients (0.10%) in the placebo group. Adverse events coded as "depression" were reported at similar rates in CAMPRAL-treated and placebo-treated patients. Although many of these events occurred in the context of alcohol relapse, no consistent pattern of relationship between the clinical course of recovery from alcoholism and the emergence of suicidality was identified. The interrelationship between alcohol dependence, depression and suicidality is well-recognized and complex. Alcohol-dependent patients, including those patients being treated with CAMPRAL, should be monitored for the development of symptoms of depression or suicidal thinking. Families and caregivers of patients being treated with CAMPRAL should be alerted to the need to monitor patients for the emergence of symptoms of depression or suicidality, and to report such symptoms to the patient's health care provider. **Information for Patients** Physicians are advised to discuss the following issues with patients for whom they prescribe CAMPRAL. Any psychoactive drug may impair judgment, thinking, or motor skills. Patients should be cautioned about operating hazardous machinery, including automobiles, until they are reasonably certain that CAMPRAL therapy does not affect their ability to engage in such activities. Patients should be advised to notify their physician if they become pregnant or intend to become pregnant during therapy. Patients should be advised to notify their physician if they are breast-feeding. Patients should be advised to continue CAMPRAL therapy as directed, even in the event of relapse and should be reminded to discuss any renewed drinking with their physician. Patients should be advised that CAMPRAL has been shown to help maintain abstinence only when used as a part of a treatment program that includes counseling and support. **Drug Interactions** The concomitant intake of alcohol and CAMPRAL does not affect the pharmacokinetics of either alcohol or acamprosate. Pharmacokinetic studies indicate that administration of disulfiram or diazepam does not affect the pharmacokinetics of acamprosate. Co-administration of naltrexone with CAMPRAL produced a 25% increase in AUC and a 33% increase in the Cmax of acamprosate. No adjustment of dosage is recommended in such patients. The pharmacokinetics of naltrexone and its major metabolite 6-beta-naltrexol were unaffected following co-administration with CAMPRAL. Other concomitant therapies: In clinical trials, the safety profile in subjects treated with CAMPRAL concomitantly with anxiolytics, hypnotics and sedatives (including benzodiazepines), or non-opioid analgesics was similar to that of subjects taking placebo with these concomitant medications. Patients taking CAMPRAL concomitantly with antidepressants more commonly reported both weight gain and weight loss, compared with patients taking either medication alone. **Carcinogenicity, Mutagenicity and Impairment of Fertility** A carcinogenicity study was conducted in which Sprague-Dawley rats received acamprosate calcium in their diet at doses of 25, 100 or 400 mg/kg/day (0.2, 0.7 or 2.5-fold the maximum recommended human dose based on an AUC comparison). There was no evidence of an increased incidence of tumors in this carcinogenicity study in the rat. An adequate carcinogenicity study in the mouse has not been conducted. Acamprosate calcium was negative in all genetic toxicology studies conducted. Acamprosate calcium demonstrated no evidence of genotoxicity in an *in vitro* bacterial reverse point mutation assay (Ames assay) or an *in vitro* mammalian cell gene mutation test using Chinese Hamster Lung V79 cells. No clastogenicity was observed in an *in vitro* chromosomal aberration assay in human lymphocytes and no chromosomal damage detected in an *in vivo* mouse micronucleus assay. Acamprosate calcium had no effect on fertility after treatment for 70 days prior to mating in male rats and for 14 days prior to mating, throughout mating, gestation and lactation in female rats at doses up to 1000 mg/kg/day (approximately 4 times the maximum recommended human daily oral dose on a mg/m² basis). In mice, acamprosate calcium administered orally for 60 days prior to mating and throughout gestation in females at doses up to 2400 mg/kg/day (approximately 5 times the maximum recommended human daily oral dose on a mg/m² basis) had no effect on fertility. **Pregnancy Category C Teratogenic Effects** Acamprosate calcium has been shown to be teratogenic in rats when given in doses that are approximately equal to the human dose (on a mg/m² basis) and in rabbits when given in doses that are approximately 3 times the human dose (on a mg/m² basis). Acamprosate calcium produced a dose-related increase in the number of fetuses with malformations in rats at oral doses of 300 mg/kg/day or greater (approximately equal to the maximum recommended human daily oral dose on a mg/m² basis). The malformations included hydronephrosis, malformed iris, retinal dysplasia, and retroesophageal subclavian artery. No findings were observed at an oral dose of 50 mg/kg/day (approximately one-fifth the maximum recommended human daily oral dose on a mg/m² basis). An increased incidence of hydronephrosis was also noted in Burgundy Tawny rabbits at oral doses of 400 mg/kg/day or greater (approximately 3 times the maximum recommended human daily oral dose on a mg/m² basis). No developmental effects were observed in New Zealand white rabbits at oral doses up to 1000 mg/kg/day (approximately 8 times the maximum recommended human daily oral dose on a mg/m² basis). The findings in animals should be considered in relation to known adverse developmental effects of ethyl alcohol, which include the characteristics of fetal alcohol syndrome (craniofacial dysmorphism, intrauterine and postnatal growth retardation, retarded psychomotor and intellectual development) and milder forms of neurological and behavioral disorders in humans. There are no adequate and well controlled studies in pregnant women. CAMPRAL should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus. **Nonteratogenic Effects** A study conducted in pregnant mice that were administered acamprosate calcium by the oral route starting on Day 15 of gestation through the end of lactation on postnatal day 28 demonstrated an increased incidence of still-born fetuses at doses of 960 mg/kg/day or greater (approximately 2 times the maximum recommended human daily oral dose on a mg/m² basis). No effects were observed at a dose of 320 mg/kg/day (approximately one-half the maximum recommended human daily dose on a mg/m² basis). **Labor and Delivery** The potential for CAMPRAL to affect the duration of labor and delivery is unknown. **Nursing Mothers** In animal studies, acamprosate was excreted in the milk of lactating rats dosed orally with acamprosate calcium. The concentration of acamprosate in milk compared to blood was 1.3:1. It is not known whether acamprosate is excreted in human milk. Because many drugs are excreted in human milk, caution should be exercised when CAMPRAL is administered to a nursing woman. **Pediatric Use** The safety and efficacy of CAMPRAL have not been established in the pediatric population. **Geriatric Use** Forty-one of the 4234 patients in double-blind, placebo-controlled, clinical trials of CAMPRAL were 65 years of age or older, while none were 75 years of age or over. There were too few patients in the ≥65 age group to evaluate any differences in safety or effectiveness for geriatric patients compared to younger patients. This drug is known to be substantially excreted by the kidney, and the risk of toxic reactions to this drug may be greater in patients with impaired renal function. Because elderly patients are more likely to have decreased renal function, care should be taken in dose selection, and it may be useful to monitor renal function (See CLINICAL PHARMACOLOGY, ADVERSE REACTIONS, and DOSAGE AND ADMINISTRATION).

ADVERSE REACTIONS
The adverse event data described below reflect the safety experience in over 7000 patients exposed to CAMPRAL for up to one year, including over 2000 CAMPRAL-exposed patients who participated in placebo-controlled trials. **Adverse Events Leading to Discontinuation** In placebo-controlled trials of 6 months or less, 8% of CAMPRAL-treated patients discontinued treatment due to an adverse event, as compared to 6% of patients treated with placebo. In studies longer than 6 months, the discontinuation rate due to adverse events was 7% in both the placebo-treated and the CAMPRAL-treated patients. Only diarrhea was associated with the discontinuation of more than 1% of patients (2% of CAMPRAL-treated vs. 0.7% of placebo-treated patients). Other events, including nausea, depression, and anxiety, while accounting for discontinuation in less than 1% of patients, were nevertheless more commonly cited in association with discontinuation in CAMPRAL-treated patients than in placebo-treated patients. **Common Adverse Events Reported in Controlled Trials** Common, non-serious adverse events were collected spontaneously in some controlled studies and using a checklist in other studies. The overall profile of adverse events was similar using either method. Table 1 shows those events that occurred in any CAMPRAL treatment group at a rate of 3% or greater and greater than the placebo group in controlled clinical trials with spontaneously reported adverse events. The reported frequencies of adverse events represent the proportion of individuals who experienced, at least once, a treatment-emergent adverse event of the type listed, without regard to the causal relationship of the events to the drug.

Table 1. Events Occurring at a Rate of at Least 3% and Greater than Placebo in any CAMPRAL Treatment Group in Controlled Clinical Trials with Spontaneously Reported Adverse Events

Body System/ Preferred Term	CAMPRAL 1332 mg/day	CAMPRAL 1998 mg/day[1]	CAMPRAL Pooled[2]	Placebo
Number of Patients in Treatment Group	**397**	**1539**	**2019**	**1706**
Number (%) of Patients with an AE	**248(62%)**	**910(59%)**	**1231(61%)**	**955(56%)**
Body as a Whole	**121(30%)**	**513(33%)**	**685(34%)**	**517(30%)**
Accidental Injury*	17 (4%)	44 (3%)	70 (3%)	52 (3%)
Asthenia	29 (7%)	79 (5%)	114(6%)	93 (5%)
Pain	6 (2%)	56 (4%)	65 (3%)	55 (3%)
Digestive System	**85 (21%)**	**440(29%)**	**574(28%)**	**344(20%)**
Anorexia	20 (5%)	35 (2%)	57 (3%)	44 (3%)
Diarrhea	39 (10%)	257(17%)	329(16%)	166(10%)
Flatulence	4 (1%)	55 (4%)	63 (3%)	28 (2%)
Nausea	11 (3%)	69 (4%)	87 (4%)	58 (3%)
Nervous System	**150(38%)**	**417(27%)**	**598(30%)**	**500(29%)**
Anxiety**	32 (8%)	80 (5%)	118(6%)	98 (6%)
Depression	33 (8%)	63 (4%)	102(5%)	87 (5%)
Dizziness	15 (4%)	49 (3%)	67 (3%)	44 (3%)
Dry mouth	13 (3%)	23 (1%)	36 (2%)	28 (2%)
Insomnia	34 (9%)	94 (6%)	137(7%)	121(7%)
Paresthesia	11 (3%)	29 (2%)	40 (2%)	34 (2%)
Skin and Appendages	**26 (7%)**	**150(10%)**	**187(9%)**	**169(10%)**
Pruritus	12 (3%)	68 (4%)	82 (4%)	58 (3%)
Sweating	11 (3%)	27 (2%)	40 (2%)	39 (2%)

*includes events coded as "fracture" by sponsor; **includes events coded as "nervousness" by sponsor
[1] includes 258 patients treated with acamprosate calcium 2000 mg/day, using a different dosage strength and regimen. [2] includes all patients in the first two columns as well as 83 patients treated with acamprosate calcium 3000 mg/day, using a different dosage strength and regimen.

Other Events Observed During the Premarketing Evaluation of CAMPRAL
Following is a list of terms that reflect treatment-emergent adverse events reported by patients treated with CAMPRAL in 20 clinical trials (4461 patients treated with CAMPRAL, 3526 of whom received the maximum recommended dose of 1998 mg/day for up to one year in duration). This listing does not include those events already listed above; events for which a drug cause was considered remote; event terms which were so general as to be uninformative; and events reported only once which were not likely to be acutely life-threatening.
Events are further categorized by body system and listed in order of decreasing frequency according to the following definitions: frequent adverse events are those occurring in at least 1/100 patients (only those not already listed in the summary of adverse events in controlled trials appear in this listing); infrequent adverse events are those occurring in 1/100 to 1/1000 patients; rare events are those occurring in fewer than 1/1000 patients. **Body as a Whole** – *Frequent:* headache, abdominal pain, back pain, infection, flu syndrome, chest pain, chills, suicide attempt; *Infrequent:* fever, intentional overdose, malaise, allergic reaction, abscess, neck pain, hernia, intentional injury; *Rare:* ascites, face edema, photosensitivity reaction, abdomen enlarged, sudden death. **Cardiovascular System** – *Frequent:* palpitation, syncope; *Infrequent:* hypotension, tachycardia, hemorrhage, angina pectoris, migraine, varicose vein, myocardial infarct, phlebitis, postural hypotension; *Rare:* heart failure, mesenteric arterial occlusion, cardiomyopathy, deep thrombophlebitis, shock. **Digestive System** – *Frequent:* vomiting, dyspepsia, constipation, increased appetite; *Infrequent:* liver function tests abnormal, gastroenteritis, gastritis, dysphagia, eructation, gastrointestinal hemorrhage, pancreatitis, rectal hemorrhage, liver cirrhosis, esophagitis, hematemesis, nausea and vomiting, hepatitis; *Rare:* melena, stomach ulcer, cholecystitis, colitis, duodenal ulcer, mouth ulceration, carcinoma of liver. **Endocrine System** – *Rare:* goiter, hypothyroidism. **Hemic and Lymphatic System** – *Infrequent:* anemia, ecchymosis, eosinophilia, lymphocytosis, thrombocytopenia; *Rare:* leukopenia, lymphadenopathy, monocytosis. **Metabolic and Nutritional Disorders** – *Frequent:* peripheral edema, weight gain; *Infrequent:* weight loss, hyperglycemia, SGOT increased, SGPT increased, gout, thirst, hyperuricemia, diabetes mellitus, avitaminosis, bilirubinemia; *Rare:* alkaline phosphatase increased, creatinine increased, hyponatremia, lactic dehydrogenase increased. **Musculoskeletal System** – *Frequent:* myalgia, arthralgia; *Infrequent:* leg cramps; *Rare:* rheumatoid arthritis, myopathy. **Nervous System** – *Frequent:* somnolence, libido decreased, amnesia, thinking abnormal, tremor, vasodilatation, hypertension; *Infrequent:* convulsion, confusion, libido increased, vertigo, withdrawal syndrome, apathy, suicidal ideation, neuralgia, hostility, agitation, neurosis, abnormal dreams, hallucinations, hypesthesia; *Rare:* alcohol craving, psychosis, hyperkinesia, twitching, depersonalization, increased salivation, paranoid reaction, torticollis, encephalopathy, manic reaction. **Respiratory System** – *Frequent:* rhinitis, cough increased, dyspnea, pharyngitis, bronchitis; *Infrequent:* asthma, epistaxis, pneumonia; *Rare:* laryngismus, pulmonary embolus. **Skin and Appendages** – *Frequent:* rash; *Infrequent:* acne, eczema, alopecia, maculopapular rash, dry skin, urticaria, exfoliative dermatitis, vesiculobullous rash; *Rare:* psoriasis. **Special Senses** – *Frequent:* abnormal vision, taste perversion; *Infrequent:* tinnitus, amblyopia, deafness; *Rare:* ophthalmitis, diplopia, photophobia. **Urogenital System** – *Frequent:* impotence; *Infrequent:* metrorrhagia, urinary frequency, urinary tract infection, sexual function abnormal, urinary incontinence, vaginitis; *Rare:* kidney calculus, abnormal ejaculation, hematuria, menorrhagia, nocturia, polyuria, urinary urgency. **Serious Adverse Events Observed During the Non-US Postmarketing Evaluation of CAMPRAL (acamprosate calcium)** Although no causal relationship to CAMPRAL has been found, the serious adverse event of acute kidney failure has been reported to be temporally associated with CAMPRAL treatment in at least 3 patients and is not described elsewhere in the labeling.

DRUG ABUSE AND DEPENDENCE
Controlled Substance Class Acamprosate calcium is not a controlled substance. **Physical and Psychological Dependence** CAMPRAL did not produce any evidence of withdrawal symptoms in patients in clinical trials at therapeutic doses. Post marketing data, collected retrospectively outside the U.S., have provided no evidence of CAMPRAL abuse or dependence.

OVERDOSAGE
In all reported cases of acute overdosage with CAMPRAL (total reported doses of up to 56 grams of acamprosate calcium), the only symptom that could be reasonably associated with CAMPRAL was diarrhea. Hypercalcemia has not been reported in cases of acute overdose. A risk of hypercalcemia should be considered in chronic overdosage only. Treatment of overdose should be symptomatic and supportive.

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Coalition Starts Autism Genetics Research Plan

Federal health agencies have teamed up with private organizations and government health agencies in Canada and Ireland to provide funding for research into the genetic basis of susceptibility to autistic spectrum disorders.

The coalition, headed by the National Institute of Mental Health, has made $21 million available to researchers and requested grant applications that focus on using large data sets of more than 1,000 pedigrees that already have been assembled. These data sets should have adequate statistical power to detect autism susceptibility loci, according to the NIMH.

Studies have located several chromosomal regions associated with autism, but few specific genes have been identified. This project asks investigators to determine the functional significance of any genes or gene variants that are identified during the analysis of the large data sets.

The identification of new genes or gene variants may help researchers to subdivide the autism spectrum disorders into distinct disorders with different molecular mechanisms.

Some of the grant applications also may address the possibility that not all heritable traits of autism directly involve alterations in the genetic code. Heritable changes that do not alter the DNA sequence include epigenetic mechanisms such as imprinting, DNA methylation, and changes in chromatin or protein conformations; they could potentially regulate gene expression and play an important etiologic role in the disorder.

—Jeff Evans