

# Lancet Withdraws Article on Vaccine's Safety

BY JOYCE FRIEDEN

The U.K. medical journal the Lancet has taken the unusual step of withdrawing an article it published—a study of 12 children with behavioral disorders that developed following administration of vaccines or the onset of measles or otitis media.

“Following the judgment of the U.K. General Medical Council [GMC] Fitness

to Practise Panel on Jan. 28, 2010, it has become clear that several elements of the 1998 paper by Wakefield et al. are incorrect, contrary to the findings of an earlier investigation,” the Lancet editors said in a statement. “In particular, the claims in the original paper that children were ‘consecutively referred’ and that investigations were ‘approved’ by the local ethics committee have been proven to be false. Therefore we fully retract

this paper from the published record.”

The Wakefield study involved 12 children described in the journal as having been consecutively referred to the pediatric gastroenterology department at the Royal Free Hospital and School of Medicine in London (Lancet 1998;351:637-41). All had a history of a pervasive developmental disorder with loss of acquired skills. They also had intestinal symptoms, including diarrhea,

abdominal pain, bloating, and food intolerance. “Investigations were approved by the Ethical Practices Committee of the Royal Free Hospital NHS Trust, and parents gave informed consent,” the authors wrote.

The researchers took histories, including details of immunizations and exposure to infectious diseases as well as developmental histories.

They also performed a battery of tests, including colonoscopy with multiple biopsies, cerebral MRI, and EEG. Lab tests were performed to rule out known causes of childhood neurodegenerative disorders.

No subjects were found to have neurological abnormalities on clinical ex-

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amination; all MRI scans, EEGs, and cerebrospinal-fluid profiles were normal, and none of the boys had fragile X syndrome.

Early development milestones had been achieved by 11 of 12 children, with the exception of one girl found to have coarctation of the aorta and who progressed rapidly after that condition was corrected at 14 months.

Behavioral diagnoses for the children included autism (9), possible postviral or vaccinal encephalitis (2) and disintegrative psychosis (1).

In eight children, parents or physicians linked the onset of behavioral problems to receiving the MMR vaccine. Five children had immediate adverse vaccine reactions including rash, fever, delirium, and in three cases, convulsions.

One subject had received monovalent measles vaccine at 15 months, after which his development slowed. He later received a dose of the MMR vaccine at age 4 years 5 months, a day after which his mother described “striking deterioration in his behavior that she did link with the immunization,” the researchers noted.

On endoscopy, the caecum was seen in all cases, and the ileum in all but two. Four cases showed the “red halo” sign around swollen caecal lymphoid follicles, an early endoscopic feature of Crohn’s disease. The researchers said the “most striking and consistent feature” was lymphoid nodular hyperplasia of the terminal ileum in 10 subjects.

The researchers noted that “intestinal and behavioral pathologies may have occurred together by chance, reflecting a selection bias in a self-referred group; however, the uniformity of the intestinal pathological changes and the fact that previous studies have found intestinal dysfunction in children with autistic spectrum disorders suggests that the con-

*Continued on following page*

effect, Intentional Injury, Retroperitoneal Fibrosis, Shock. Cardiovascular System – *Inrequent*: Deep thrombophlebitis, Heart failure, Hypotension, Postural hypotension, Retinal vascular disorder, Syncope; *Rare*: ST Depressed, Ventricular Fibrillation. Digestive System – *Frequent*: Gastroenteritis, Increased appetite; *Inrequent*: Cholecystitis, Cholelithiasis, Colitis, Dysphagia, Esophagitis, Gastritis, Gastrointestinal hemorrhage, Melena, Mouth ulceration, Pancreatitis, Rectal hemorrhage, Tongue edema; *Rare*: Aphthous stomatitis, Esophageal Ulcer, Periodontal abscess. Hemic and Lymphatic System – *Frequent*: Echinomycosis; *Inrequent*: Anemia, Eosinophilia, Hypochromic anemia, Leukocytosis, Leukopenia, Lymphadenopathy, Thrombocytopenia; *Rare*: Myelofibrosis, Polycythemia, Prothrombin decreased, Purpura, Thrombocytopenia. Metabolic and Nutritional Disorders – *Rare*: Glucose Tolerance Decreased, Urate Crystalluria. Musculoskeletal System – *Frequent*: Arthralgia, Leg cramps, Myalgia, Myasthenia; *Inrequent*: Arthrosis; *Rare*: Chondrodystrophy, Generalized Spasm. Nervous System – *Frequent*: Anxiety, Depersonalization, Hypertonia, Hypesthesia, Libido decreased, Nystagmus, Paresthesia, Stupor, Twitching; *Inrequent*: Abnormal dreams, Agitation, Apathy, Aphasia, Circumoral paresthesia, Dysarthria, Hallucinations, Hostility, Hyperalgesia, Hyperesthesia, Hyperkinesia, Hypokinesia, Hypotonia, Libido increased, Myoclonus, Neuralgia; *Rare*: Addiction, Cerebellar syndrome, Cogwheel rigidity, Coma, Delirium, Delusions, Dysautonomia, Dyskinesia, Dystonia, Encephalopathy, Extrapyramidal syndrome, Guillain-Barré syndrome, Hypalgesia, Intracranial hypertension, Manic reaction, Paranoid reaction, Peripheral neuritis, Personality disorder, Psychotic depression, Schizophrenic reaction, Sleep disorder, Torticollis, Trismus. Respiratory System – *Rare*: Apnea, Atelectasis, Bronchiolitis, Hiccup, Laryngismus, Lung edema, Lung fibrosis, Yawn. Skin and Appendages – *Frequent*: Pruritus; *Inrequent*: Alopecia, Dry skin, Eczema, Hirsutism, Skin ulcer, Urticaria, Vesiculobullous rash; *Rare*: Angioedema, Exfoliative dermatitis, Lichenoid dermatitis, Melanosis, Nail Disorder, Peticial rash, Purpuric rash, Pustular rash, Skin atrophy, Skin necrosis, Skin nodule, Stevens-Johnson syndrome, Subcutaneous nodule. Special senses – *Frequent*: Conjunctivitis, Diplopia, Otitis media, Tinnitus; *Inrequent*: Abnormality of accommodation, Blepharitis, Dry eyes, Eye hemorrhage, Hyperacusis, Photophobia, Retinal edema, Taste loss, Taste perversion; *Rare*: Anisocoria, Blindness, Corneal ulcer, Exophthalmos, Extraocular palsy, Iritis, Keratitis, Keratoconjunctivitis, Miosis, Mydriasis, Night blindness, Ophthalmoplegia, Optic atrophy, Papilledema, Parosmia, Ptosis, Uveitis. Urogenital System – *Frequent*: Anorgasmia, Impotence, Urinary frequency, Urinary incontinence; *Inrequent*: Abnormal ejaculation, Albuminuria, Amenorrhea, Dysmenorrhea, Dysuria, Hematuria, Kidney calculus, Leukorrhea, Menorrhagia, Metrorrhagia, Nephritis, Oliguria, Urinary retention, Urine abnormality; *Rare*: Acute kidney failure, Balanitis, Bladder Neoplasm, Cervicitis, Dyspareunia, Epididymitis, Female lactation, Glomerulitis, Ovarian disorder, Pylonephritis.

**Comparison of Gender and Race** The overall adverse event profile of pregabalin was similar between women and men. There are insufficient data to support a statement regarding the distribution of adverse experience reports by race.

**Post-marketing Experience** The following adverse reactions have been identified during postapproval use of LYRICA. Because these reactions are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to drug exposure. Nervous System Disorders – Headache. Gastrointestinal Disorders – Nausea, Diarrhea.

## DRUG INTERACTIONS

Since LYRICA is predominantly excreted unchanged in the urine, undergoes negligible metabolism in humans (<2% of a dose recovered in urine as metabolites), and does not bind to plasma proteins, its pharmacokinetics are unlikely to be affected by other agents through metabolic interactions or protein binding displacement. *In vitro* and *in vivo* studies showed that LYRICA is unlikely to be involved in significant pharmacokinetic drug interactions. Specifically, there are no pharmacokinetic interactions between pregabalin and the following antiepileptic drugs: carbamazepine, valproic acid, lamotrigine, phenytoin, phenobarbital, and topiramate. Important pharmacokinetic interactions would also not be expected to occur between LYRICA and commonly used antiepileptic drugs. **Pharmacodynamics** Multiple oral doses of LYRICA were co-administered with oxycodone, lorazepam, or ethanol. Although no pharmacokinetic interactions were seen, additive effects on cognitive and gross motor functioning were seen when LYRICA was co-administered with these drugs. No clinically important effects on respiration were seen.

## USE IN SPECIFIC POPULATIONS

**Pregnancy** Pregnancy Category C. Increased incidences of fetal structural abnormalities and other manifestations of developmental toxicity, including lethality, growth retardation, and nervous and reproductive system functional impairment, were observed in the offspring of rats and rabbits given pregabalin during pregnancy, at doses that produced plasma pregabalin exposures (AUC)  $\geq 5$  times human exposure at the maximum recommended dose (MRD) of 600 mg/day. When pregnant rats were given pregabalin (500, 1250, or 2500 mg/kg) orally throughout the period of organogenesis, incidences of specific skull alterations attributed to abnormally advanced ossification (premature fusion of the jugal and nasal sutures) were increased at  $\geq 1250$  mg/kg, and incidences of skeletal variations and retarded ossification were increased at all doses. Fetal body weights were decreased at the highest dose. The low dose in this study was associated with a plasma exposure (AUC) approximately 17 times human exposure at the MRD of 600 mg/day. A no-effect dose for rat embryo-fetal developmental toxicity was not established. When pregnant rabbits were given LYRICA (250, 500, or 1250 mg/kg) orally throughout the period of organogenesis, decreased fetal body weight and increased incidences of skeletal malformations, visceral variations, and retarded ossification were observed at the highest dose. The no-effect dose for developmental toxicity in rabbits (500 mg/kg) was associated with a plasma exposure approximately 16 times human exposure at the MRD. In a study in which female rats were dosed with LYRICA (50, 100, 250, 1250, or 2500 mg/kg) throughout gestation and lactation, offspring growth was reduced at  $\geq 100$  mg/kg and offspring survival was decreased at  $\geq 250$  mg/kg. The effect on offspring survival was pronounced at doses  $\geq 1250$  mg/kg, with 100% mortality in high-dose litters. When offspring were tested as adults, neurobehavioral abnormalities (decreased auditory startle responding) were observed at  $\geq 250$  mg/kg and reproductive impairment (decreased fertility and litter size) was seen at 1250 mg/kg. The no-effect dose for pre- and postnatal developmental toxicity in rats (50 mg/kg) produced a plasma exposure approximately 2 times human exposure at the MRD. There are no adequate and well-controlled studies in pregnant women. LYRICA should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus. To provide information regarding the effects of in utero exposure to LYRICA, physicians are advised to recommend that pregnant patients taking LYRICA enroll in the North American Antiepileptic Drug (NAAED) Pregnancy Registry. This can be done by calling the toll free number 1-888-233-2334, and must be done by patients themselves. Information on the registry can also be found at the website <http://www.aedpregnancyregistry.org/>. **Labor and Delivery** The effects of LYRICA on labor and delivery in pregnant women are unknown. In the prenatal-postnatal study in rats, pregabalin prolonged gestation and induced dystocia at exposures  $\geq 5$  times the mean human exposure (AUC<sub>0-24</sub> of 123  $\mu\text{g}\cdot\text{hr}/\text{mL}$ ) at the maximum recommended clinical dose of 600 mg/day. **Nursing Mothers** It is not known if pregabalin is excreted in human milk; it is, however, present in the milk of rats. Because many drugs are excreted in human milk, and because of the potential for tumorigenicity shown for pregabalin in animal studies, a decision should be made whether to discontinue nursing or to discontinue the drug, taking into account the importance of the drug to the mother. **Pediatric Use** The safety and efficacy of pregabalin in pediatric patients have not been established. In studies in which pregabalin (50 to 500 mg/kg) was orally administered to young rats from early in the postnatal period (Postnatal Day 7) through sexual maturity, neurobehavioral abnormalities (deficits in learning and memory, altered locomotor activity, decreased auditory startle responding and habituation) and reproductive impairment (delayed sexual maturation and decreased fertility in males and females) were observed at doses  $\geq 50$  mg/kg. The neurobehavioral changes of acoustic startle persisted at  $\geq 250$  mg/kg and locomotor activity and water maze performance at  $\geq 500$  mg/kg in animals tested after cessation of dosing and, thus, were considered to represent long-term effects. The low effect dose for developmental neurotoxicity and reproductive impairment in juvenile rats (50 mg/kg) was associated with a plasma pregabalin exposure (AUC) approximately equal to human exposure at the maximum recommended dose of 600 mg/day. A no-effect dose was not established. **Geriatric Use** In controlled clinical studies of LYRICA in fibromyalgia, 106 patients were 65 years of age or older. Although the adverse reaction profile was similar between the two age groups, the following neurological adverse reactions were more frequent in patients 65 years of age or older: dizziness, vision blurred, balance disorder, tremor, confusional state, coordination abnormal, and lethargy. LYRICA is known to be substantially excreted by the kidney, and the risk of toxic reactions to LYRICA may be greater in patients with impaired renal function. Because LYRICA is eliminated primarily by renal excretion, the dose should be adjusted for elderly patients with renal impairment.

## DRUG ABUSE AND DEPENDENCE

**Controlled Substance** LYRICA is a Schedule V controlled substance. LYRICA is not known to be active at receptor sites associated with drugs of abuse. As with any CNS active drug, physicians should carefully evaluate patients for history of drug abuse and observe them for signs of LYRICA misuse or abuse (e.g., development of tolerance, dose escalation, drug-seeking behavior). **Abuse** In a study of recreational users (N=15) of sedative/hypnotic drugs, including alcohol, LYRICA (450 mg, single dose) received subjective ratings of “good drug effect,” “high” and “liking” to a degree that was similar to diazepam (30 mg, single dose). In controlled clinical studies in over 5500 patients, 4% of LYRICA-treated patients and 1% of placebo-treated patients overall reported euphoria as an adverse reaction, though in some patient populations studied, this reporting rate was higher and ranged from 1 to 12%. **Dependence** In clinical studies, following abrupt or rapid discontinuation of LYRICA, some patients reported symptoms including insomnia, nausea, headache or diarrhea [see *Warnings and Precautions*], suggestive of physical dependence.

## OVERDOSAGE

**Signs, Symptoms and Laboratory Findings of Acute Overdosage in Humans** There is limited experience with overdose of LYRICA. The highest reported accidental overdose of LYRICA during the clinical development program was 8000 mg, and there were no notable clinical consequences. In clinical studies, some patients took as much as 2400 mg/day. The types of adverse reactions experienced by patients exposed to higher doses ( $\geq 900$  mg) were not clinically different from those of patients administered recommended doses of LYRICA. **Treatment or Management of Overdose** There is no specific antidote for overdose with LYRICA. If indicated, elimination of unabsorbed drug may be attempted by emesis or gastric

lavage; usual precautions should be observed to maintain the airway. General supportive care of the patient is indicated including monitoring of vital signs and observation of the clinical status of the patient. A Certified Poison Control Center should be contacted for up-to-date information on the management of overdose with LYRICA. Although hemodialysis has not been performed in the few known cases of overdose, it may be indicated by the patient’s clinical state or in patients with significant renal impairment. Standard hemodialysis procedures result in significant clearance of pregabalin (approximately 50% in 4 hours).

## NONCLINICAL TOXICOLOGY

**Carcinogenesis, Mutagenesis, Impairment of Fertility** **Carcinogenesis** A dose-dependent increase in the incidence of malignant vascular tumors (hemangiosarcomas) was observed in two strains of mice (B6C3F1 and CD-1) given pregabalin (200, 1000, or 5000 mg/kg) in the diet for two years. Plasma pregabalin exposure (AUC) in mice receiving the lowest dose that increased hemangiosarcomas was approximately equal to the human exposure at the maximum recommended dose (MRD) of 600 mg/day. A no-effect dose for induction of hemangiosarcomas in mice was not established. No evidence of carcinogenicity was seen in two studies in Wistar rats following dietary administration of pregabalin for two years at doses (50, 150, or 450 mg/kg in males and 100, 300, or 900 mg/kg in females) that were associated with plasma exposures in males and females up to approximately 14 and 24 times, respectively, human exposure at the MRD. **Mutagenesis** Pregabalin was not mutagenic in bacteria or in mammalian cells *in vitro*, was not clastogenic in mammalian systems *in vitro* and *in vivo*, and did not induce unscheduled DNA synthesis in mouse or rat hepatocytes. **Impairment of Fertility** In fertility studies in which male rats were orally administered pregabalin (50 to 2500 mg/kg) prior to and during mating with untreated females, a number of adverse reproductive and developmental effects were observed. These included decreased sperm counts and sperm motility, increased sperm abnormalities, reduced fertility, increased preimplantation embryo loss, decreased litter size, decreased fetal body weights, and an increased incidence of fetal abnormalities. Effects on sperm and fertility parameters were reversible in studies of this duration (3–4 months). The no-effect dose for male reproductive toxicity in these studies (100 mg/kg) was associated with a plasma pregabalin exposure (AUC) approximately 3 times human exposure at the maximum recommended dose (MRD) of 600 mg/day. In addition, adverse reactions on reproductive organ (testes, epididymides) histopathology were observed in male rats exposed to pregabalin (500 to 1250 mg/kg) in general toxicology studies of four weeks or greater duration. The no-effect dose for male reproductive organ histopathology in rats (250 mg/kg) was associated with a plasma exposure approximately 8 times human exposure at the MRD. In a fertility study in which female rats were given pregabalin (500, 1250, or 2500 mg/kg) orally prior to and during mating and early gestation, disrupted estrous cyclicity and an increased number of days to mating were seen at all doses, and embryolethality occurred at the highest dose. The low dose in this study produced a plasma exposure approximately 9 times that in humans receiving the MRD. A no-effect dose for female reproductive toxicity in rats was not established. **Human Data** In a double-blind, placebo-controlled clinical trial to assess the effect of pregabalin on sperm motility, 30 healthy male subjects were exposed to pregabalin at a dose of 600 mg/day. After 3 months of treatment (one complete sperm cycle), the difference between placebo- and pregabalin-treated subjects in mean percent sperm with normal motility was <4% and neither group had a mean change from baseline of more than 2%. Effects on other male reproductive parameters in humans have not been adequately studied.

**Animal Toxicology and/or Pharmacology** **Dermatopathy** Skin lesions ranging from erythema to necrosis were seen in repeated-dose toxicity studies in both rats and monkeys. The etiology of these skin lesions is unknown. At the maximum recommended human dose (MRD) of 600 mg/day, there is a 2-fold safety margin for the dermatological lesions. The more severe dermatopathies involving necrosis were associated with pregabalin exposures (as expressed by plasma AUCs) of approximately 3 to 8 times those achieved in humans given the MRD. No increase in incidence of skin lesions was observed in clinical studies. **Ocular Lesions** Ocular lesions (characterized by retinal atrophy [including loss of photoreceptor cells] and/or corneal inflammation/mineralization) were observed in two lifetime carcinogenicity studies in Wistar rats. These findings were observed at plasma pregabalin exposures (AUC)  $\geq 2$  times those achieved in humans given the maximum recommended dose of 600 mg/day. A no-effect dose for ocular lesions was not established. Similar lesions were not observed in lifetime carcinogenicity studies in two strains of mice or in monkeys treated for 1 year.



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nection is real and reflects a unique disease process.”

Despite consistent gastrointestinal findings, behavioral changes in these children were not consistent, the authors wrote. “In some cases the onset and course of behavioral regression was precipitous, with children losing all communication skills over a few weeks to months.”

They added that their study “did not prove an association between measles, mumps, and rubella vaccine and the syndrome described... . If there is a causal link between measles, mumps, and rubella vaccine and this syndrome, a rising incidence might be anticipated after the introduction of this vaccine in the [United Kingdom] in 1988. Published evidence is inadequate to show whether there is a change in incidence or a link with measles, mumps, and rubella vaccine.”

According to its report, the GMC panel found that in 1996, Dr. Wakefield was involved in advising Richard Barr, an attorney acting on behalf of people alleged to have suffered harm caused by the administration of the MMR vaccine, “as to the research that would be required to establish that the vaccine was causing injury.” The panel found that “[Dr. Wakefield’s] involvement in the MMR litigation... had ethical implications and should have been disclosed.”

Similarly, it found that Dr. Wakefield should have disclosed that he received 50,000 pounds (\$78,000) in funding for the study from the Legal Aid Board—from a grant that Mr. Barr applied for. In helping Mr. Barr apply for the money, Dr. Wakefield did not disclose to the Legal Aid Board that some of the items that money was being requested for, such as MRI studies, were already being paid for by Britain’s National Health Service, the board found.

Regarding the Lancet paper, the panel found that Dr. Wakefield’s describing the referral process as “routine” when some of the patients were actually specifically selected for the study “was irresponsible and misleading and contrary to [his] duty as a senior author.”

The panel also noted that four of the children in the study lacked a history of gastrointestinal symptoms, thereby making them unlikely “routine referrals” to the hospital’s gastroenterology department, and that Dr. Wakefield should have disclosed to the Lancet that in 1997, he filed for a patent on a new MMR vaccine.

In the case of one of the children in the study, the panel also found that Dr. Wakefield “ordered the neurophysiological investigations without having requisite paediatric qualifications and writing an incorrect diagnosis on the investigation form.”

The panel also noted that Dr. Wakefield paid some children who were guests at his son’s birthday party £5 (\$8) to have their blood taken as part of the study; it noted that this showed “a callous disregard for the distress and pain that [Dr. Wakefield] knew or ought to have known the children involved might suffer.”

In addition to its statement on the withdrawal of the article, the Lancet’s editors also released a 2004 comment from the Royal Free and University College Medical School and the Royal Free Hampstead NHS Trust stating that they were “entirely satisfied that the investigations performed on the children reported in the Lancet paper had been subjected to appropriate and rigorous ethical scrutiny. Because the nature of the condition affecting child behavior and gastroenterological symptoms was unknown and required elucidation, the investigation of these children was prop-

erly submitted to and fully discussed by the Ethical Practices Committee at the Royal Free Hampstead in 1996... . The clinical management and investigation of these children was performed at the Free by a dedicated team of consultant pediatric gastroenterologists, in full consultation with and agreement of the parents of the affected children” (Lancet 2004;363:824).

Does The Lancet’s withdrawal of the paper help vaccination advocates? “I think the retraction is far too little far too late,” Dr. Paul Offit, chief of the division of infectious diseases and the director of

the Vaccine Education Center at the Children’s Hospital of Philadelphia, said in an interview.

“The Lancet published a hypothesis that was unsupported and has since been disproven by careful scientific study. But there is no undoing the harm of that original paper. Many parents abandoned the MMR vaccine. As a consequence, hundreds of children were hospitalized and four were killed by measles. This retraction will do nothing to change that,” Dr. Offit continued.

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