

Gonorrhea Drug Resistance Could Lead to Crisis

BY BETSY BATES

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SAN DIEGO — Resistance to gonorrhea drugs is climbing just as treatment options are dwindling, making for a potential public health crisis if more drug choices are not brought to market soon.

“The situation is really not good. We’re hanging by a thread, with a very serious resistance problem. If we lose cephalosporins [to resistance], we will really

be up a creek,” Dr. Jeanne Marrazzo said at Perspectives in Women’s Health, sponsored by FAMILY PRACTICE NEWS, OB.GYN. NEWS, and INTERNAL MEDICINE NEWS.

Practically speaking, ceftriaxone (125 mg intramuscularly, in a single dose) remains the only available regimen recommended by the Centers for Disease Control and Prevention for treating gonorrhea, the second-most commonly reported infectious disease in the United States.

After years of decline or stability, U.S.

rates of gonorrhea rose for the second straight year in 2006, with about 358,000 new cases reported, according to CDC surveillance statistics.

Many infectious disease specialists are wary of dependence on a single drug to treat a widespread infectious disease because of the threat of resistance, and gonorrhea seems particularly susceptible.

Widespread resistance long ago took penicillins, sulfa drugs, tetracycline, and spectinomycin off the table for gonococ-

cal infections; by April of last year, fluoroquinolones, including ciprofloxacin, ofloxacin, and levofloxacin, also lost their “recommended” status because of resistance documented in sites in the United States and other countries.

Cefixime remains on the CDC’s recommended list; it is currently unavailable in the United States, except in a liquid pediatric formula approved last year. A problem with the pediatric formula is that it has a limited shelf life once reconstituted.

Dr. Marrazzo explained that Wyeth Pharmaceuticals discontinued manufacture of cefixime tablets, once marketed as Suprax, when the patent for the medication expired in 2002.

Exclusive rights to the drug are now held by a company based in India, which is rumored to be working with the Food and Drug Administration to obtain approval to market 400-mg tablets in the United States.

Alternative regimens suggested by the CDC include spectinomycin, which is also

Depression	2	2	2	2	2	2
Respiratory, Thoracic and Mediastinal Disorders						
Pharyngolaryngeal pain	2	1	3	3	2	2

*PGB: pregabalin

Other Adverse Reactions Observed During the Clinical Studies of LYRICA Following is a list of treatment-emergent adverse reactions reported by patients treated with LYRICA during all clinical trials. The listing does not include those events already listed in the previous tables or elsewhere in labeling, those events for which a drug cause was remote, those events which were so general as to be uninformative, and those events reported only once which did not have a substantial probability of being acutely life-threatening. Events are categorized by body system and listed in order of decreasing frequency according to the following definitions: *frequent* adverse reactions are those occurring on one or more occasions in at least 1/100 patients; *infrequent* adverse reactions are those occurring in 1/100 to 1/1000 patients; *rare* reactions are those occurring in fewer than 1/1000 patients. Events of major clinical importance are described in the *Warnings and Precautions* section. Body as a Whole — *Frequent*: Abdominal pain, Allergic reaction, Fever, *Infrequent*: Abscess, Cellulitis, Chills, Malaise, Neck rigidity, Overdose, Pelvic pain, Photosensitivity reaction, Suicide attempt, *Rare*: Anaphylactoid reaction, Ascites, Granuloma, Hangover effect, Intentional Injury, Retroperitoneal Fibrosis, Shock, Suicide. Cardiovascular System — *Infrequent*: Deep thrombophlebitis, Heart failure, Hypotension, Postural hypotension, Retinal vascular disorder, Syncope, *Rare*: ST Depressed, Ventricular Fibrillation. Digestive System — *Frequent*: Gastroenteritis, Increased appetite, *Infrequent*: Cholecystitis, Cholelithiasis, Colitis, Dysphagia, Esophagitis, Gastritis, Gastrointestinal hemorrhage, Melena, Mouth ulceration, Pancreatitis, Rectal hemorrhage, Tongue edema, *Rare*: Aphthous stomatitis, Esophageal Ulcer, Peridontal abscess. Hemic and Lymphatic System — *Frequent*: Echinomiasis, *Infrequent*: 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, *Infrequent*: Arthrosis, *Rare*: Chondrodystrophy, Generalized Spasm. Nervous System — *Frequent*: Anxiety, Depersonalization, Hypertonia, Hypesthesia, Libido decreased, Nystagmus, Paresthesia, Stupor, Twitching, *Infrequent*: 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, Extrapyrmidal 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, Bronchitis, Hiccup, Laryngismus, Lung edema, Lung fibrosis, Yawn. Skin and Appendages — *Frequent*: Pruritus, *Infrequent*: Alopecia, Dry skin, Eczema, Hirsutism, Skin ulcer, Urticaria, Vesiculobullous rash, *Rare*: Angioedema, Exfoliative dermatitis, Lichenoid dermatitis, Melanosis, Nail Disorder, Petechial rash, Purpuric rash, Pustular rash, Skin atrophy, Skin necrosis, Skin nodule, Stevens-Johnson syndrome, Subcutaneous nodule. Special senses — *Frequent*: Conjunctivitis, Diplopia, Otitis media, Tinnitus, *Infrequent*: Abnormality of accommodation, Blepharitis, Dry eyes, Eye hemorrhage, Hyperacusis, Photophobia, Retinal edema, Taste loss, Taste perversion, *Rare*: Anisocoria, Blindness, Corneal ulcer, Exophthalmos, Extradural palsy, Iritis, Keratitis, Keratoconjunctivitis, Miosis, Mydriasis, Night blindness, Ophthalmoplegia, Optic atrophy, Papilledema, Parosmia, Ptosis, Uveitis. Urogenital System — *Frequent*: Anorgasmia, Impotence, Urinary frequency, Urinary incontinence, *Infrequent*: 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, Pyelonephritis. **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

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) ≥ 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 ≥ 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 ≥ 100 mg/kg and offspring survival was decreased at ≥ 250 mg/kg. The effect on offspring survival was pronounced at doses ≥ 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 ≥ 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. **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 ≥ 50 times the mean human exposure (AUC (0-24) 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 ≥ 50 mg/kg. The neurobehavioral changes of acoustic startle persisted

at ≥ 250 mg/kg and locomotor activity and water maze performance at ≥ 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 neuropathic pain associated with diabetic peripheral neuropathy, 246 patients were 65 to 74 years of age, and 73 patients were 75 years of age or older. In controlled clinical studies of LYRICA in neuropathic pain associated with postherpetic neuralgia, 282 patients were 65 to 74 years of age, and 379 patients were 75 years of age or older. In controlled clinical studies of LYRICA in epilepsy, there were only 10 patients 65 to 74 years of age, and 2 patients who were 75 years of age or older. No overall differences in safety and efficacy were observed between these patients and younger patients. 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 [see *Dosage and Administration*].

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 (450mg, single dose) received subjective ratings of “good drug effect,” “high” and “liking” to a degree that was similar to diazepam (30mg, 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 Overdose 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 (≥ 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).

PATIENT COUNSELING INFORMATION

Patient Package Insert Patients should be informed of the availability of a patient information leaflet, and they should be instructed to read the leaflet prior to taking LYRICA. **Angioedema** Patients should be advised that LYRICA may cause angioedema, with swelling of the face, mouth (lip, gum, tongue) and neck (larynx and pharynx) that can lead to life-threatening respiratory compromise. Patients should be instructed to discontinue LYRICA and immediately seek medical care if they experience these symptoms [see *Warnings and Precautions*]. **Hypersensitivity** Patients should be advised that LYRICA has been associated with hypersensitivity reactions such as wheezing, dyspnea, rash, hives, and blisters. Patients should be instructed to discontinue LYRICA and immediately seek medical care if they experience these symptoms [see *Warnings and Precautions*]. **Dizziness and Somnolence** Patients should be counseled that LYRICA may cause dizziness, somnolence, blurred vision and other CNS signs and symptoms. Accordingly, they should be advised not to drive, operate complex machinery, or engage in other hazardous activities until they have gained sufficient experience on LYRICA to gauge whether or not it affects their mental, visual, and/or motor performance adversely [see *Warnings and Precautions*]. **Weight Gain and Edema** Patients should be counseled that LYRICA may cause edema and weight gain. Patients should be advised that concomitant treatment with LYRICA and a thiazolidinedione antidiabetic agent may lead to an additive effect on edema and weight gain. For patients with preexisting cardiac conditions, this may increase the risk of heart failure [see *Warnings and Precautions*]. **Abrupt or Rapid Discontinuation** Patients should be advised to take LYRICA as prescribed. Abrupt or rapid discontinuation may result in insomnia, nausea, headache, or diarrhea [see *Warnings and Precautions*]. **Ophthalmological Effects** Patients should be counseled that LYRICA may cause visual disturbances. Patients should be informed that if changes in vision occur, they should notify their physician [see *Warnings and Precautions*]. **Creatine Kinase Elevations** Patients should be instructed to promptly report unexplained muscle pain, tenderness, or weakness, particularly if accompanied by malaise or fever [see *Warnings and Precautions*]. **CNS Depressants** Patients who require concomitant treatment with central nervous system depressants such as opiates or benzodiazepines should be informed that they may experience additive CNS side effects, such as somnolence. **Alcohol** Patients should be told to avoid consuming alcohol while taking LYRICA, as LYRICA may potentiate the impairment of motor skills and sedating effects of alcohol. **Use in Pregnancy** Patients should be instructed to notify their physician if they become pregnant or intend to become pregnant during therapy, and to notify their physician if they are breast feeding or intend to breast feed during therapy [see *Use in Specific Populations*]. **Male Fertility** Men being treated with LYRICA who plan to father a child should be informed of the potential risk of male-mediated teratogenicity. In preclinical studies in rats, pregabalin was associated with an increased risk of male-mediated teratogenicity. The clinical significance of this finding is uncertain. **Dermatopathy** Diabetic patients should be instructed to pay particular attention to skin integrity while being treated with LYRICA. Some animals treated with pregabalin developed skin ulcerations, although no increased incidence of skin lesions associated with LYRICA was observed in clinical trials.



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LYRICA
PREGABALIN

capsules

Pfizer U.S. Pharmaceuticals

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A cervical smear photomicrograph shows extracellular diplococci determined to be *Neisseria gonorrhoeae* bacteria.

no longer being manufactured in the United States, and single-dose cephalosporin regimens.

All patients with gonorrhea should be cotreated for chlamydia unless it is ruled out with a highly sensitive test.

The lack of availability of spectinomycin complicates management of patients allergic to cephalosporins, according to Dr. Marrazzo of the Seattle STD/HIV Prevention Training Center and the University of Washington, Seattle. The CDC “cluelessly” recommends desensitizing patients, a suggestion she considers impractical in a busy clinic.

Such cases might call for special consideration of high-dose azithromycin, but the 2-g dose required can cause gastrointestinal problems, even with split doses administered several hours apart. In any case, resistance to azithromycin is likely increasing, so “that’s going to be a short-term fix.”

If fluoroquinolones are the only remaining option in cephalosporin-allergic patients, Dr. Marrazzo recommends obtaining a culture before treatment to ensure sensitivity, or obtaining a test of cure in 3-5 days by culture or 3 weeks if a nucleic acid amplification test is used.

Dr. Marrazzo disclosed that she is a consultant to Mission Pharmacal, and serves on the speakers bureaus of 3M and Merck & Co. INTERNAL MEDICINE NEWS is published by International Medical News Group, a division of Elsevier.