

Bioterrorism and Vaccine Events Remain Threats

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SCOTTSDALE, ARIZ. — Despite the grateful lull that has followed Sept. 11 and the anthrax scare in 2001, bioterrorism remains a very real threat, according to a Food and Drug Administration counterterrorism official.

Dr. Boris Lushniak, the FDA's assistant commissioner for counterterrorism policy and assistant U.S. surgeon general, hopes

that vigilance remains active in medical offices and emergency departments across the United States—but he has his doubts.

"I daresay we are going to be caught off guard," Dr. Lushniak said during the Alfred L. Weiner Lecture at the annual meeting of the Noah Worcester Dermatological Society.

A disturbing number of organisms meet all or some of the criteria for an ideal agent of biological terrorism: easy to obtain and work with, inexpensive to produce, able to

be widely disseminated, fairly stable in the environment, capable of producing high morbidity and mortality, transmissible from person to person, and difficult to diagnose and treat, which would allow an attack to quickly overwhelm the health care system.

On a positive note, the U.S. government has now stockpiled enough vaccine against smallpox to inoculate every man, woman, and child in the country, Dr. Lushniak reported.

On the other hand, when U.S. public health authorities were notified recently about an individual with suspicious skin lesions on an inbound flight from China, they were unable to find any hospital in a major metropolitan area willing to admit and quarantine the 200 people aboard until danger to the public was ruled out.

Fortunately, in that case, the threat was nullified during 4 hours of frantic planning as the airliner approached U.S. shores, but it stands as a wake-up call about preparedness. "We really have to change the way we do our business," he said.

The potential agents of greatest concern—labeled category A by the Centers for Disease Control and Prevention—remain the same as ever: anthrax, smallpox, plague, tularemia, viral hemorrhagic fevers, and botulinum toxin.

"All suspicious or confirmed cases should be reported to health authorities immediately," Dr. Lushniak said.

"We should all have that high level of suspicion. If you're worried, if you think it's part of your differential, you really should give someone a call. It may be a false alarm, may be overreading, but ... really what we're looking for is someone to be able to ring that first fire alarm," he said.

The timing could be critical.

Anthrax, for example, can be controlled with antibiotics if it is recognized and treated with postexposure prophylaxis before protein-rich toxins are produced by the organism. "If you can nip it in the spore bud, so to speak, then you really have solved the problem," he said.

The disease is heralded by a flulike prodrome, progressing to hypoxia, dyspnea, and, often, mediastinal widening on x-ray.

He reminded dermatologists of the clinical presentation of cutaneous anthrax exposure following a 1- to 12-day incubation period. The presenting symptom might be tender pruritic macules that evolve into papules, which progress to vesicles and bullae formation in 24-48 hours. Bullae may rupture when they reach 1-2 cm. Eventually, telltale black necrotic ulcers may be seen, with a black eschar visible by day 6.

Differential diagnoses for cutaneous anthrax include brown recluse spider bites, ecthyma gangrenosum, tularemia, staph infections, and herpes labialis.

If smallpox is ever used in a bioterrorist attack, the tip-off may be its severe prodrome, which follows a noninfectious incubation period lasting 7-17 days, Dr. Lushniak said.

For 2-4 days, infected patients have very high fevers (101° F-104° F), prostration, myalgias, and malaise as small red macules and papules begin to form and even ulcerate on the tongue and mouth. An exanthem then appears in a centrifugal pat-

tern on the face, arms, hands, legs, and feet. Macules form, then papules. By day 5, tense, often umbilicated vesicles can be seen that look like "BB pellets embedded in the skin," he noted.

By day 6-12, pustules begin to form crusts that remain intact throughout a long period of infection until they separate at about day 28, leaving depressed scars.

Differential diagnoses include varicella, molluscum contagiosum, hand-foot-and-mouth disease, disseminated herpes simplex virus, herpes zoster, pustular drug eruptions, and scabies.

"If this were to come back into the world, the feeling is that at least the prodrome may keep people at home, in bed," he said.

Even preventive efforts aimed at a potential bioterrorism attack have health implications that physicians should recognize, Dr. Lushniak said.

He described a 2007 case of household transmission of the live virus through a smallpox vaccine. Within a month of the father having received a smallpox vaccination prior to military deployment overseas, he came into contact with his infant son, who had eczema.

Although the father's vaccine site was covered during the unplanned visit, the child developed a high fever and a generalized papular, vesicular rash that began on the head and neck. Within days, umbilicated lesions covered more than 50% of the child's body and he required mechanical ventilation.

After a course of antiviral and vasopressor medications, intravenous immunoglobulin, and supportive therapy, the child was discharged from the hospital—48 days after admission.

His mother, who had rested her head on the child's chest at one point, also developed a mild vesicular rash on her face.

Cell cultures in the home found evidence of the virus on a booster seat, a toy, and a slipper.

"This ain't real smallpox, people!" Dr. Lushniak said to emphasize the high level of transmission there would be in an actual attack, and the importance of then having a "ring" vaccination strategy aimed at everyone in contact with an exposed subject within 3-4 days.

LEXAPRO® (escitalopram oxalate) TABLETS/ORAL SOLUTION

(5% and 4%); Fatigue (5% and 2%). **Psychiatric Disorders:** Insomnia (9% and 4%); Somnolence (6% and 2%); Appetite Decreased (3% and 1%); Libido Decreased (3% and 1%). **Respiratory System Disorders:** Rhinitis (5% and 4%); Sinusitis (3% and 2%). **Urogenital:** Ejaculation Disorder* (9% and <1%); Impotence* (3% and <1%); Anorgasmia* (2% and <1%). *Events reported by at least 2% of patients treated with Lexapro are reported, except for the following events which had an incidence on placebo > Lexapro: headache, upper respiratory tract infection, back pain, pharyngitis, inflicted injury, anxiety. †Primarily ejaculatory delay. ‡Denominator used was for males only (N=225 Lexapro; N=188 placebo). †Denominator used was for females only (N=490 Lexapro; N=404 placebo). **Generalized Anxiety Disorder Table 3** enumerates the incidence, rounded to the nearest percent of treatment-emergent adverse events that occurred among 429 GAD patients who received Lexapro 10 to 20 mg/day in placebo-controlled trials. Events included are those occurring in 2% or more of patients treated with Lexapro and for which the incidence in patients treated with Lexapro was greater than the incidence in placebo-treated patients. The most commonly observed adverse events in Lexapro patients (incidence of approximately 5% or greater and approximately twice the incidence in placebo patients) were nausea, ejaculation disorder (primarily ejaculatory delay), insomnia, fatigue, decreased libido, and anorgasmia (see TABLE 3). **TABLE 3. Treatment-Emergent Adverse Events: Incidence in Placebo-Controlled Clinical Trials for Generalized Anxiety Disorder* (Percentage of Patients Reporting Event) Body System/Adverse Event (Lexapro (N=429) and Placebo (N=427)).** **Autonomic Nervous System Disorders:** Dry Mouth (9% and 5%); Sweating Increased (4% and 1%). **Central & Peripheral Nervous System Disorders:** Headache (24% and 17%); Paresthesia (2% and 1%). **Gastrointestinal Disorders:** Nausea (18% and 8%); Diarrhea (8% and 6%); Constipation (5% and 4%); Indigestion (3% and 2%); Vomiting (3% and 1%); Abdominal Pain (2% and 1%); Flatulence (2% and 1%); Toothache (2% and 0%). **General:** Fatigue (8% and 2%); Influenza-like symptoms (5% and 4%). **Musculoskeletal:** Neck/Shoulder Pain (3% and 1%). **Psychiatric Disorders:** Somnolence (13% and 7%); Insomnia (12% and 6%); Libido Decreased (7% and 2%); Dreaming Abnormal (3% and 2%); Appetite Decreased (3% and 1%); Lethargy (3% and 1%); Yawning (2% and 1%). **Urogenital:** Ejaculation Disorder* (14% and 2%); Anorgasmia* (6% and <1%); Menstrual Disorder (2% and 1%). *Events reported by at least 2% of patients treated with Lexapro are reported, except for the following events which had an incidence on placebo > Lexapro: inflicted injury, dizziness, back pain, upper respiratory tract infection, rhinitis, pharyngitis. †Denominator used was for males only (N=182 Lexapro; N=195 placebo). ‡Denominator used was for females only (N=247 Lexapro; N=232 placebo). **Dose Dependency of Adverse Events** The potential dose dependency of common adverse events (defined as an incidence rate of ≥ 5% in either the 10 mg or 20 mg Lexapro groups) was examined on the basis of the combined incidence of adverse events in two fixed-dose trials. The overall incidence rates of adverse events in 10 mg Lexapro-treated patients (66%) was similar to that of the placebo-treated patients (61%), while the incidence rate in 20 mg/day Lexapro-treated patients was greater (86%). **Table 4** shows common adverse events that occurred in the 20 mg/day Lexapro group with an incidence that was approximately twice that of the 10 mg/day Lexapro group and approximately twice that of the placebo group. **TABLE 4. Incidence of Common Adverse Events* in Patients with Major Depressive Disorder Receiving Placebo (N=311), 10 mg/day Lexapro (N=310), 20 mg/day Lexapro (N=125).** **Insomnia** (4%, 7%, 14%); **Diarrhea** (5%, 6%, 14%); **Dry Mouth** (3%, 4%, 9%); **Somnolence** (1%, 4%, 9%); **Dizziness** (2%, 4%, 7%); **Sweating Increased** (<1%, 3%, 8%); **Constipation** (1%, 3%, 6%); **Fatigue** (2%, 2%, 6%); **Indigestion** (1%, 2%, 6%). *Adverse events with an incidence rate of at least 5% in either of the Lexapro groups and with an incidence rate in the 20 mg/day Lexapro group that was approximately twice that of the 10 mg/day Lexapro group and the placebo group. **Male and Female Sexual Dysfunction with SSRIs** Although changes in sexual desire, sexual performance, and sexual satisfaction often occur as manifestations of a psychiatric disorder, they may also be a consequence of pharmacologic treatment. In particular, some evidence suggests that SSRIs can cause such untoward sexual experiences. Reliable estimates of the incidence and severity of untoward experiences involving sexual desire, performance, and satisfaction are difficult to obtain, however, in part because patients and physicians may be reluctant to discuss them. Accordingly, estimates of the incidence of untoward sexual experience and performance cited in product labeling are likely to underestimate their actual incidence. **Table 5** shows the incidence rates of sexual side effects in patients with major depressive disorder and GAD in placebo-controlled trials. **TABLE 5. Incidence of Sexual Side Effects in Placebo-Controlled Clinical Trials (In Males Only; Adverse Event: Lexapro (N=407) and Placebo (N=383)).** Ejaculation Disorder (primarily ejaculatory delay) (12% and 1%); Libido Decreased (6% and 2%); Impotence (2% and <1%). (In Females Only: Lexapro (N=737) and Placebo (N=636)). Libido Decreased (3% and 1%); Anorgasmia (3% and <1%) There are no adequately designed studies examining sexual dysfunction with escitalopram treatment. Priapism has been reported with all SSRIs. While it is difficult to know the precise risk of sexual dysfunction associated with the use of SSRIs, physicians should routinely inquire about such possible side effects. **Vital Sign Changes** Lexapro and placebo groups were compared with respect to (1) mean change from baseline in vital signs (pulse, systolic blood pressure, and diastolic blood pressure) and (2) the incidence of patients meeting criteria for potentially clinically significant changes from baseline in these variables. These analyses did not reveal any clinically important changes in vital signs associated with Lexapro treatment. In addition, a comparison of supine and standing vital sign measures in subjects receiving Lexapro indicated that Lexapro treatment is not associated with orthostatic changes. **Weight Changes** Patients treated with Lexapro in controlled trials did not differ from placebo-treated patients with regard to clinically important change in body weight. **Laboratory Changes** Lexapro and placebo groups were compared with respect to (1) mean change from baseline in various serum chemistry, hematology, and urinalysis variables, and (2) the incidence of patients meeting criteria for potentially clinically significant changes from baseline in these variables. These analyses revealed no clinically important changes in laboratory test parameters associated with Lexapro treatment. **ECG Changes** Electrocardiograms from Lexapro (N=625), racemic citalopram (N=351), and placebo (N=527) groups were compared with respect to (1) mean change from baseline in various ECG parameters and (2) the incidence of patients meeting criteria for potentially clinically significant changes from baseline in these variables. These analyses revealed (1) a decrease in heart rate of 2.2 bpm for Lexapro and 2.7 bpm for racemic citalopram, compared to an increase of 0.3 bpm for placebo and (2) an increase in QTc interval of 3.9 msec for Lexapro and 3.7 msec for racemic citalopram, compared to 0.5 msec for placebo. Neither Lexapro nor racemic citalopram were associated with the development of clinically significant ECG abnormalities. **Other Events Observed During the Premarketing Evaluation of Lexapro** Following is a list of WHO terms that reflect treatment-emergent adverse events, as defined in the introduction to the ADVERSE REACTIONS section, reported by the 1428 patients treated with Lexapro for periods of up to one year in double-blind or open-label clinical trials during its premarketing evaluation. All reported events are included except those already listed in Tables 2 & 3, those occurring in only one patient, event terms that are so general as to be uninformative, and those that are unlikely to be drug related. It is important to emphasize that, although the events reported occurred during treatment with Lexapro, they were not necessarily caused by it. 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 on one or more occasions in at least 1/100 patients; infrequent adverse events are those occurring in less than 1/100 patients but at least 1/1000 patients. **Cardiovascular - Frequent:** palpitation, hypertension. **Infrequent:** bradycardia, tachycardia, ECG abnormal, flushing, varicose vein. **Central and Peripheral Nervous System Disorders - Frequent:** light-headed feeling, migraine. **Infrequent:** tremor, vertigo, restless legs, shaking, twitching, dysequilibrium, tics, carpal tunnel syndrome, muscle contractions involuntary, sluggishness, coordination abnormal, faintness, hyperreflexia, muscular tone increased. **Gastrointestinal Disorders - Frequent:** heartburn, abdominal cramp, gastroenteritis. **Infrequent:** gastroesophageal reflux, bloating, abdominal discomfort, dyspepsia, increased stool frequency, belching, gastritis, hemorrhoids, gagging, polyposis gastric, swallowing difficult. **General - Frequent:** allergy, pain in limb, fever, hot flushes, chest pain. **Infrequent:** edema of extremities, chills, tightness of chest, leg pain, asthenia, syncope, malaise, anaphylaxis, fall. **Hemic and Lymphatic Disorders - Frequent:** bruise, anemia, nosebleed, hematoma, lymphadenopathy cervical. **Metabolic and Nutritional Disorders - Frequent:** increased weight. **Infrequent:** decreased weight, hyperglycemia, thirst, bilirubin increased, hepatic enzymes increased, gout, hypercholesterolemia. **Musculoskeletal System Disorders - Frequent:** arthralgia, myalgia. **Infrequent:** jaw stiffness, muscle cramp, muscle stiffness, arthritis, muscle weakness, back discomfort, arthropathy, jaw pain, joint stiffness. **Psychiatric Disorders - Frequent:** appetite increased, lethargy, irritability, concentration impaired. **Infrequent:** jitteriness, panic reaction, agitation, apathy, forgetfulness, depression aggravated, nervousness, restlessness aggravated, suicide attempt, amnesia, anxiety attack, brounism, carbohydrate craving, confusion, depersonalization, disorientation, emotional lability, feeling unreal, tremulousness nervous, crying abnormal, depression, excitability, auditory hallucination, suicidal tendency. **Reproductive Disorders-Female* - Frequent:** menstrual cramps, menstrual disorder. **Infrequent:** menorrhagia, breast neoplasm, pelvic inflammation, premenstrual syndrome, spotting between menses. *% based on female subjects only; N=905. **Respiratory System Disorders - Frequent:** bronchitis, sinus congestion, coughing, nasal congestion, sinus headache. **Infrequent:** asthma, breath shortness, laryngitis, pneumonia, tracheitis. **Skin and Appendages Disorders - Frequent:** rash. **Infrequent:** pruritus, acne, alopecia, eczema, dermatitis, dry skin, folliculitis, lipoma, furunculosis, dry lips, skin nodule. **Special Senses - Frequent:** vision blurred, tinnitus. **Infrequent:** taste alteration, earache, conjunctivitis, vision abnormal, dry eyes, eye irritation, visual disturbance, eye infection, pupils dilated, metallic taste. **Urinary System Disorders - Frequent:** urinary frequency, urinary tract infection. **Infrequent:** urinary urgency, kidney stone, dysuria, blood in urine. **Events Reported Subsequent to the Marketing of Escitalopram** - Although no causal relationship to escitalopram treatment has been found, the following adverse events have been reported to have occurred in patients and to be temporally associated with escitalopram treatment during post marketing spontaneous and clinical trial experience and were not observed during the premarketing evaluation of escitalopram: Blood and Lymphatic System Disorders: hemolytic anemia, leukopenia, thrombocytopenia. Cardiac Disorders: atrial fibrillation, cardiac failure, myocardial infarction, torsade de pointes, ventricular arrhythmia, ventricular tachycardia. Endocrine Disorders: diabetes mellitus, hyperprolactinemia, SIADH. Eye Disorders: diplopia, glaucoma. Gastrointestinal Disorders: gastrointestinal hemorrhage, pancreatitis, rectal hemorrhage. General Disorders and Administration Site Conditions: abnormal gait, Hepatobiliary Disorders: fulminant hepatitis, hepatic failure, hepatic necrosis, hepatitis. Immune System Disorders: allergic reaction. Investigations: electrocardiogram QT prolongation, INR increased, prothrombin decreased. Metabolism and Nutrition Disorders: hypoglycemia, hypokalemia. Musculoskeletal and Connective Tissue Disorders: rhabdomyolysis. Nervous System Disorders: akathisia, choreoathetosis, dysarthria, dyskinesia, dystonia, extrapyramidal disorders, grand mal seizures (or convulsions), hypoaesthesia, myoclonus, neuroleptic malignant syndrome, nystagmus, seizures, serotonin syndrome, tardive dyskinesia. Pregnancy, Puerperium and Perinatal Conditions: spontaneous abortion. Psychiatric Disorders: acute psychosis, aggression, anger, delirium, delusion, nightmare, paranoia, visual hallucinations. Renal and Urinary Disorders: acute renal failure. Reproductive System and Breast Disorders: priapism. Respiratory, Thoracic and Mediastinal Disorders: pulmonary embolism. Skin and Subcutaneous Tissue Disorders: angioedema, ecchymosis, erythema multiforme, photosensitivity reaction, Stevens Johnson Syndrome, toxic epidermal necrolysis, urticaria. Vascular Disorders: deep vein thrombosis, hypertension, orthostatic hypotension, phlebitis thrombosis. Forest Pharmaceuticals, Inc. Subsidiary of Forest Laboratories, Inc. 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Bioterrorism Prevention Steps

- ▶ Learn more by going to www.bt.cdc.gov.
- ▶ Join the civilian volunteer Medical Reserve Corps and participate in disaster response in your community (www.medicalreservecorps.gov).
- ▶ Train and deploy with a National Disaster Medical Assistance Team (www.hhs.gov/aspr/opeo/ndms/teams/dmat.html).
- ▶ Join the active reserve corps of the U.S. Public Health Service (<http://usphs-ppac.org>).

Source: Dr. Lushniak