How to monitor medication side effects

Jon E. Grant, JD, MD, MPH

Woman prescribed a stimulant suffers stroke and disability

Harris County (TX) District Court

A 39-year-old patient was diagnosed with attention-deficit/hyperactivity disorder (ADHD) by a psychologist, who referred her to a psychiatrist. The psychiatrist prescribed amphetamine/dextroamphetamine, which the patient took for 9 months. During this time her blood pressure and other vital signs were not monitored. The patient then suffered a stroke, is now a paraplegic, and must use a wheelchair.

The patient claimed that negligent misdiagnosis and monitoring caused the stroke. The psychiatrist maintained that diagnosis and monitoring were appropriate, and the drug did not cause the stroke. The psychiatrist also claimed that the patient had a transient ischemic attack (TIA) before taking amphetamine/dextroamphetamine and another stroke after discontinuing the drug.

> A defense verdict was returned

Improper dose of lamotrigine blamed for liver failure

San Diego County (CA) Superior Court

The patient, age 35, was involuntarily admitted to an inpatient psychiatric facility after the police found her acting bizarrely and hallucinating. The admitting and treating psychiatrist learned that the patient had been admitted for psychiatric treatment 9 times in the previous 12 months, had a long history of polysubstance abuse, and had been largely nonadherent with medication. The psychiatrist diagnosed rapid-cycling bipolar disorder and started the patient on lamotrigine with an escalating dosage schedule. The patient was released from the psychiatric facility.

Later that month, the patient developed a urinary tract infection and was readmitted to the hospital. She agreed to lab testing and all results were within normal limits, but throughout a 2-month stay the patient intermittently complained of a sore throat, cough, and nausea. Two weeks later, the psychiatrist reviewed lab tests that showed a mild elevation of the patient's liver enzymes.

The next day the patient reported a rash on her chest and a high fever. She was transferred to an acute care facility. The patient's liver enzymes continued to rise, and the psychiatrist discontinued lamotrigine. The patient continued to deteriorate and was transferred to another hospital to consult with a liver specialist. About 3 weeks later the patient went into a coma and died.

Autopsy showed massive liver necrosis. The patient's family claimed the psychiatrist was negligent in giving the patient lamotrigine, which caused the liver failure. They contended the dose prescribed was too high, the patient was not properly monitored,

Cases are selected by Current Psychiatry from *Medical Malpractice Verdicts, Settlements & Experts*, with permission of its editor, Lewis Laska of Nashville, TN (www.verdictslaska.com). Information may be incomplete in some instances, but these cases represent clinical situations that typically result in litigation.

Dr. Grant is associate professor of psychiatry, University of Minnesota Medical Center, Minneapolis.

and other psychiatric drugs could have been used with more gradual increases.

The psychiatrist maintained that the lamotrigine dosage used was appropriate, lamotrigine was not known to cause liver problems, and it did not cause the patient's liver failure.

> A defense verdict was returned

Dr. Grant's observations

These cases reflect a clinician's worst nightmare—using an appropriate medication, experiencing a disastrous outcome, and then being sued for malpractice. Clinicians need to remember:

- anyone can be sued
- a lawsuit does not mean that the clinician did anything inappropriate.

It is unfortunate that such lawsuits are brought, and their presence may indicate many problems within the legal system. Although clinicians who do nothing wrong should not have to endure unnecessary and unfounded lawsuits (the issue of tort reform within the legal system is beyond the scope of this column), these cases prompt psychiatrists to consider ways to protect themselves from such claims. Some practices might help protect you from successful malpractice claims, but there are no guarantees.

Meeting standards of care

Medical malpractice claims could be based on a physician diverging from 1 of 2 standards of care:

- The "average practitioner" or "customary practice" standard means the treatment practice is consistent with others in the field. Courts might allow the medical profession to define the standard of care according to medical custom.
- The "reasonably prudent physician" standard means what a reasonable physician would have done under the circumstances. The jury determines if the physician acted reasonably, not whether the physician conformed to existing standards.[1]

States are split on which standard the courts must apply and in many areas, the standard of care is based on local—not state or national—practices.[2]

In these cases, using amphetamine/dextroamphetamine for ADHD and lamotrigine for bipolar disorder appears to meet either standard. These 2 drugs are FDA-approved to treat the disorders for which they were prescribed. Although we do not know what doses the physicians prescribed in these 2 cases, in general if the dosing adheres to the FDA-approved range or can be based on credible research, the treatment will meet the 2 standards.

Choosing a treatment plan

The American Psychiatric Association's practice guidelines state "the ultimate judgment regarding a particular clinical procedure or treatment plan must be made by the psychiatrist in light of the clinical data presented by the patient and the diagnostic and treatment options available."[3]

Regardless of the treatment used—even if the medication is "off-label" and not FDA-approved for a particular disorder or the dose is not within the FDA-approved dosing range—you should be able to document your rationale for using a medication and dosing by showing that it is part of good clinical practice.

A clinician's scientific rationale for medication and dosing choice should be based on the psychiatric evaluation and known risks and benefits of the treatment. In addition, the patient should:

- understand pertinent information regarding the medication and its side effects
- and freely give consent to treatment.[4]

Then document in the patient's chart that you had this discussion with the patient and obtained consent.

continued

Clinical Point

In general if dosing is in the FDA-approved range or is based on credible research, the treatment will meet the standard of care

Monitoring for side effects

In these cases, the court also had to determine whether clinicians' monitoring for side effects was appropriate. For several years, case reports have raised speculation about a link between strokes and amphetamine/dextroamphetamine.[4,5] In 2005, Adderall XR was taken off the Canadian market because of reports of strokes and sudden deaths.[7]

The FDA's Adverse Event Reporting System database identified 12 cases of sudden death in pediatric patents treated for ADHD with Adderall or Adderall XR.[8] Although the drug has returned to the Canadian market and a clear link between stroke or sudden death and Adderall has not been established, *The Physicians' Desk Reference* (PDR)[9] advises physicians to monitor blood pressure in individuals taking amphetamine/dextroamphetamine, particularly those with hypertension. The FDA has issued new labeling instructions for all stimulants advising prescribing clinicians to monitor blood pressure regularly.[10]

Adverse side effects are possible with any number of medications. Clinicians might need to change assessments and monitoring practices as new information—such as FDA or pharmaceutical company reporting or new studies in professional journals—becomes available.

Even so, if you fail to monitor blood pressure and a patient has a stroke—such as in the first case—you are not necessarily negligent. Successful malpractice cases need to demonstrate causation. The plaintiff must prove:

- The physician's act or omission was the cause-in-fact of the harm. Without the act, the harm would not have occurred.
- The act was the proximate cause of the harm. In a natural, unbroken sequence of events, the act produces a foreseeable result. A physician should not be liable for the far-reaching and improbable consequences of an act or omission.[1]

Plaintiffs cannot prove proximate cause if there is:

- lack of foreseeability—the consequences of the act were not reasonably foreseeable, or
- an intervening event that supersedes all others in causing the injury.[1]

Foreseeability

A defendant may be liable only if the consequences of the act or omission were reasonably foreseeable. Foreseeability is a vague legal concept and is not the same as predictability. Foreseeability should be understood in context of what information was available at the time. For example, the FDA black box warnings about the link between stimulants and stroke or sudden death did not appear until 2006.[11] What might be considered foreseeable now might not have been before 2006 (it is unclear when the above case was litigated).

Intervening events

An intervening event is one that takes effect after the defendant's negligence and breaks the chain of causation. In the first case, the patient had a history of TIAs before taking amphetamine/dextroamphetamine. The condition that caused the TIAs, such as atherosclerosis in an artery, may also have caused the stroke independent of the use of stimulants, and therefore could be considered an intervening event.

In the lamotrigine case, elevations of aspartate transaminase and alanine transaminase are infrequent or rare. Several case reports have discussed possible hepatotoxicity associated with the drug.[13]

A reasonably prudent physician should warn patients about and monitor for symptoms of Stevens-Johnson syndrome, a serious disorder of the skin and mucous membranes sometimes seen with lamotrigine that can begin with cough, fever, and sore throat. Although hepatitis is a possible complication of Stevens-Johnson, the first step of treatment is to hospitalize the pa-

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Clinical Point

Foreseeability is not the same as predictability and should be understood in the context of what information is available

highest dose of oral olanzapine (15±2.5 mg/d). In controlled clinical trials of intramuscular olanzapine for injection, there were no statistically significant differences from placebo in occurrence of any treatment-emergent extrapyramidal symptoms, assessed by either rating scales incidence or spontaneously reported adverse events.

Other Adverse Events: Dose-relatedness of adverse events was assessed using data from this same clinical trial involving 3 fixed oral dosage ranges (5±2.5, 10±2.5, or 15±2.5 mg/d) compared with placebo. The following treatment-emergent events showed a statistically significant trend: asthenia, dry mouth, nausea, somnolence, tremor.

In an 8-week, randomized, double-blind study in patients with schizophrenia, schizophreniform disorder, or schizoaffective disorder comparing fixed doses of 10, 20, and 40 mg/d, statistically significant differences were seen between doses for the following: baseline to endpoint weight gain, 10 vs 40 mg/d; incidence of treatment-emergent prolactin elevations >24.2 ng/mL (female) or >18.77 ng/mL (male), 10 vs 40 mg/d and 20 vs 40 mg/d; fatigue, 10 vs 40 mg/d and 20 vs 40 mg/d; and dizziness, 20 vs 40 mg/d.

Vital Sign Changes—Oral olanzapine was associated with orthostatic hypotension and tachycardia in clinical trials. Intramuscular olanzapine for injection was associated with bradycardia, hypotension, and tachycardia in clinical trials (*see* PRECAUTIONS).

Weight Gain—In placebo-controlled 6-week schizophrenia studies, weight gain was reported in 5.6% of oral olanzapine patients (average 2.8-kg gain) compared to 0.8% of placebo patients (average 0.4-kg loss); 29% of olanzapine patients gained >7% of their baseline weight, compared to 3% of placebo patients. During continuation therapy (238 median days of exposure), 56% of patients met the criterion for having gained >7% of their baseline weight. Average gain during long-term therapy was 5.4 kg.

Laboratory Changes—Olanzapine is associated with asymptomatic increases in SGPT, SGOT, and GGT and with increases in serum prolactin and CPK (*see* PRECAUTIONS). Asymptomatic elevation of eosinophils was reported in 0.3% of olanzapine patients in premarketing trials. There was no indication of a risk of clinically significant neutropenia associated with olanzapine in the premarketing database.

In clinical trials among olanzapine-treated patients with baseline random triglyceride levels of <150 mg/dL (N=659), 0.5% experienced triglyceride levels of ≥500 mg/dL anytime during the trials. In these same trials, olanzapine-treated patients (N=1185) had a mean triglyceride increase of 20 mg/dL from a mean baseline of 175 mg/dL. In placebo-controlled trials, olanzapine-treated patients with baseline random cholesterol levels of <200 mg/dL (N=1034) experienced cholesterol levels of ≥240 mg/dL anytime during the trials more often than placebo-treated patients (N=602; 3.6% vs 2.2% respectively). In these same trials, olanzapine-treated patients (N=2528) had a mean increase of 0.4 mg/dL in cholesterol from a mean baseline of 203 mg/dL, which was significantly different compared to placebo-treated patients (N=1415) with a mean decrease of 4.6 mg/dL from a mean baseline of 203 mg/dL.

ECG Changes—Analyses of pooled placebo-controlled trials revealed no statistically significant olanzapine/placebo differences in incidence of potentially important changes in ECG parameters, including QT, QTc, and PR intervals. Olanzapine was associated with a mean increase in heart rate of 2.4 BPM compared to no change among placebo patients.

Other Adverse Events Observed During Clinical Trials—The following treatment-emergent events were reported with oral olanzapine at multiple doses ≥1 mg/d in clinical trials (8661 patients, 4165 patient-years of exposure). This list may not include events previously listed elsewhere in labeling, those events for which a drug cause was remote, those terms which were so general as to be uninformative, and those events reported only once or twice which did not have a substantial probability of being acutely life-threatening. *Frequent* events occurred in ≥1/100 patients; *infrequent* events occurred in 1/100 to 1/1000 patients; *rare* events occurred in <1/1000 patients. ***Body as a Whole***—*Frequent:* dental pain, flu syndrome; *Infrequent:* abdomen enlarged, chills, face edema, intentional injury, malaise, moniliasis, neck pain, neck rigidity, pelvic pain, photosensitivity reaction, suicide attempt; *Rare:* chills and fever, hangover effect, sudden death. ***Cardiovascular***—*Frequent:* hypotension; *Infrequent:* atrial fibrillation, bradycardia, cerebrovascular accident, congestive heart failure, heart arrest, hemorrhage, migraine, pallor, palpitation, vasodilatation, ventricular extrasystoles; *Rare:* arteritis, heart failure, pulmonary embolus. ***Digestive***—*Frequent:* flatulence, increased salivation, thirst; *Infrequent:* dysphagia, esophagitis, fecal impaction, fecal incontinence, gastritis, gastroenteritis, gingivitis, hepatitis, melena, mouth ulceration, nausea and vomiting, oral moniliasis, periodontal abscess, rectal hemorrhage, stomatitis, tongue edema, tooth caries; *Rare:* aphthous stomatitis, enteritis, eructation, esophageal ulcer, glossitis, ileus, intestinal obstruction, liver fatty deposit, tongue discoloration. ***Endocrine***—*Infrequent:* diabetes mellitus; *Rare:* diabetic acidosis, goiter. ***Hemic and Lymphatic***—*Infrequent:* anemia, cyanosis, leukocytosis, leukopenia, lymphadenopathy, thrombocytopenia; *Rare:* normocytic anemia, thrombocythemia. ***Metabolic and Nutritional***—*Infrequent:* acidosis, alkaline phosphatase increased, bilirubinemia, dehydration, hypercholesteremia, hyperglycemia, hyperlipemia, hyperuricemia, hypoglycemia, hypokalemia, hyponatremia, lower extremity edema, upper extremity edema; *Rare:* gout, hyperkalemia, hypernatremia, hypoproteinemia, ketosis, water intoxication. ***Musculoskeletal***—*Frequent:* joint stiffness, twitching; *Infrequent:* arthritis, arthrosis, leg cramps, myasthenia; *Rare:* bone pain, bursitis, myopathy, osteoporosis, rheumatoid arthritis. ***Nervous System***—*Frequent:* abnormal dreams, amnesia, delusions, emotional lability, euphoria, manic reaction, paresthesia, schizophrenic reaction; *Infrequent:* akinesia, alcohol misuse, antisocial reaction, ataxia, CNS stimulation, cogwheel rigidity, delirium, dementia, depersonalization, dysarthria, facial paralysis, hypesthesia, hypokinesia, hypotonia, incoordination, libido decreased, libido increased, obsessive compulsive symptoms, phobias, somatization, stimulant misuse, stupor, stuttering, tardive dyskinesia, vertigo, withdrawal syndrome; *Rare:* circumoral paresthesia, coma, encephalopathy, neuralgia, neuropathy, nystagmus, paralysis, subarachnoid hemorrhage, tobacco misuse. ***Respiratory***—*Frequent:* dyspnea; *Infrequent:* apnea, asthma, epistaxis, hemoptysis, hyperventilation, hypoxia, laryngitis, voice alteration; *Rare:* atelectasis, hiccup, hypoventilation, lung edema, stridor. ***Skin and Appendages***—*Frequent:* sweating; *Infrequent:* alopecia, contact dermatitis, dry skin, eczema, maculopapular rash, pruritus, seborrhea, skin discoloration, skin ulcer, urticaria, vesiculobullous rash; *Rare:* hirsutism, pustular rash. ***Special Senses***—*Frequent:* conjunctivitis; *Infrequent:* abnormality of accommodation, blepharitis, cataract, deafness, diplopia, dry eyes, ear pain, eye hemorrhage, eye inflammation, eye pain, ocular muscle abnormality, taste perversion, tinnitus; *Rare:* corneal lesion, glaucoma, keratoconjunctivitis, macular hypopigmentation, miosis, mydriasis, pigment deposits lens. ***Urogenital***—*Frequent:* vaginitis*; *Infrequent:* abnormal ejaculation,* amenorrhea,* breast pain, cystitis, decreased menstruation,* dysuria, female lactation,* glycosuria, gynecomastia, hematuria, impotence,* increased menstruation,* menorrhagia,* metrorrhagia,* polyuria, premenstrual syndrome,* pyuria, urinary frequency, urinary retention, urinary urgency, urination impaired, uterine fibroids enlarged,* vaginal hemorrhage*; *Rare:* albuminuria, breast enlargement, mastitis, oliguria. (*Adjusted for gender.)

The following treatment-emergent events were reported with intramuscular olanzapine for injection at one or more doses ≥2.5 mg/injection in clinical trials (722 patients). This list may not include events previously listed elsewhere in labeling, those events for which a drug cause was remote, those terms which were so general as to be uninformative, and those events reported only once or twice which did not have a substantial probability of being acutely life-threatening. ***Body as a Whole***—*Frequent:* injection site pain; *Infrequent:* abdominal pain, fever. ***Cardiovascular***—*Infrequent:* AV block, heart block, syncope. ***Digestive***—*Infrequent:* diarrhea, nausea. ***Hemic and Lymphatic***—*Infrequent:* anemia. ***Metabolic and Nutritional***—*Infrequent:* creatine phosphokinase increased, dehydration, hyperkalemia. ***Musculoskeletal***—*Infrequent:* twitching. ***Nervous System***—*Infrequent:* abnormal gait, akathisia, articulation impairment, confusion, emotional lability. ***Skin and Appendages***—*Infrequent:* sweating.

Postintroduction Reports—Reported since market introduction and temporally (not necessarily causally) related to olanzapine therapy: allergic reaction (eg, anaphylactoid reaction, angioedema, pruritus or urticaria), diabetic coma, jaundice, neutropenia, pancreatitis, priapism, rhabdomyolysis, and venous thromboembolic events (including pulmonary embolism and deep venous thrombosis). Random cholesterol levels of ≥240 mg/dL and random triglyceride levels of ≥1000 mg/dL have been reported.

DRUG ABUSE AND DEPENDENCE: Olanzapine is not a controlled substance.

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Related Resources

Drug Brand Names

Amphetamine/Dextroamphetamine • Adderall
Lamotrigine • Lamictal

tient in an intensive care unit, which the physician did. The PDR and FDA guidelines do not recommend monitoring liver function tests as a way to assess for Stevens-Johnson or for liver dysfunction as an independent problem with lamotrigine.[9,12]

Given the lack of guidelines and the scant literature on this topic, the psychiatrist in this case would not have been expected to monitor liver function, which would meet either the "average practitioner" or "reasonably prudent physician" standard. Although the literature suggests that liver toxicity might have been foreseeable, the patient had a history of polysubstance abuse, which may be determined to be an intervening event. Substance abuse could have caused liver toxicity, depending on the drugs the patient abused.

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