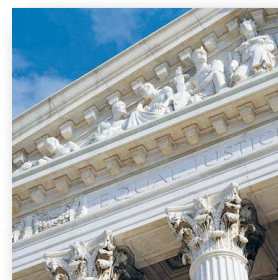


Forensic Analysis in Drug Litigation Finds Most Errors Occur with Commonly Used Therapies and Practices

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INTRODUCTION

In previous columns, we have explored various ways in which the historical basis for pharmacy and therapeutics (P&T) committees¹ accreditation requirements and litigation matters have driven the need for sound P&T committees within health care entities. The importance of rational drug-use policy was covered in this column in 2017² and the topic has gained additional exposure as a result of recent Food and Drug Administration (FDA) and Centers for Medicare and Medicaid Services (CMS) initiatives. FDA Commissioner Scott Gottlieb accelerated

Keywords: Drug injuries, litigation, negligence, drug therapy, OB-GYN, reproductive medicine, pharmacology

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Disclosure: Dr. J. T. O'Donnell and Dr. J. J. O'Donnell consult in drug injury litigation. Dr. Vogenberg reports no financial or commercial interests in regard to this article.

the approval of generic drugs, new chemical entities, and biologic drug approvals during 2018, resulting in a significant increase in the number of available products on the market.^{3,5} CMS Commissioner Sumer Verma has put out a Request for Information Notice seeking public comment regarding the appropriateness



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of some Medicare-approved accrediting organizations (AOs) offering fee-based consultative services to Medicare-participating providers and suppliers that they also accredit as part of their business model—i.e., the Joint Commission and others.⁶ Beyond cost-sharing or changing reimbursement rates for drugs, Verma has reiterated the role of managed care-associated P&T drug-product selection rules in determining coverage in Medicare programs (parts B, C, D).⁷

In public and private sector programs, pharmacy benefit manager (PBM) litigation and regulatory investigation through the Department of Health and Human Services (HHS) Health Care Fraud Prevention and Enforcement Action Team (HEAT) initiatives to prevent or reduce Medicare and Medicaid fraud have continued. Early PBM litigation was focused on formularies that favored certain drugs when the PBM was owned by the pharmaceutical manufacturer, i.e., vertical integration,⁸ which, in 2019, is eerily similar to the phenomenon of a merger between a health plan and a retail pharmacy chain. PBMs, their P&T committees, and the controversy surrounding them will remain Department of Justice targets under HEAT and the self-funded plans provided directly through alternative contracting initiatives with provider organizations (hospitals, health systems, or medical practices like Gesinger, Kaiser,

InterMountain, etc.). Helping to prevent fraud—and requiring that PBMs disclose to plan sponsors (purchasers) the cost of drugs and any benefit or payment directly or indirectly accruing to PBMs, if they make a substitution in which the substitute drug costs more than the prescribed drug—has been a focus of market change by purchasers. Such change creates more interest in and scrutiny of P&T committees from plaintiff attorneys.

ABOUT DRUG INJURIES

There is a risk of injury or complication with any drug therapy, and injuries tend to be more damaging to the patient and caregiver if the drug was selected, administered, dispensed, or monitored negligently, which usually contributes greatly to the injury. Although injury itself does not establish malpractice or negligence, drug injury litigation is common and is the second most frequent reason for medical malpractice lawsuits.⁹

For purposes of this forensic examination of drug injuries with implications for P&T committees, we focus on a high-risk group to illustrate the variety of scenarios and basic legal trends. Pregnant patients (and fetuses/newborns) are at a greater-than-average risk, given the little-known teratologic and embryo-fetal toxicity of drugs administered during pregnancy and the perinatal period.^{10,11}

DRUG INJURY CASE SUMMARIES*

1. Fatal Electrolyte Disturbance in Hyperemesis Gravidum

The patient was diagnosed in the obstetrician's office with constipation, based on having had no bowel movements in the

*[NOTE: Most cases are confidential and not disclosable, as resolutions are often confidential. Some cases were dropped after thorough analysis. One of the authors (J. T. O'Donnell) consulted in all of the cases presented here.]

previous seven days and not having eaten for seven days. She was seen in the obstetrician's office, having had nausea and vomiting for three weeks, with a 14-pound weight loss and clinical dehydration. The patient was sent from the office to the hospital. Labs were ordered immediately and a soapsuds enema (SSE) was ordered and administered. Lab results of significance were potassium (K⁺) 1.8 mEq/L and sodium (Na⁺) 121 mEq/L. Twenty mEq of potassium chloride in dextrose 5% normal saline at 50 mL/hour was ordered, and the patient was admitted to the labor and delivery unit. A second lab panel showed K⁺ of 1.5 mEq/L. However, the patient experienced a cardiac arrest 60 minutes after admission and staff were unable to resuscitate her.

Case findings showed critical K⁺ and Na⁺ levels that required immediate attention with careful and aggressive replenishment in an intensive care unit (ICU). There was slow clinical electrolyte replenishment, insufficient for treating acute/chronic severe deficiency. The severe hypokalemia created a significant risk for a fatal arrhythmia and the severe hyponatremia created a significant risk for seizures. Ultimately, treatment was "too little, too late," and the response by health care professionals was deemed to be too slow.

The case resolution/legal outcome was that the physician and hospital were sued for malpractice; insufficient clinical monitoring and care; inadequate urgency and treatment at the hospital; and failure to achieve the "standard of care." The plaintiff's obstetrician-gynecologist (ob-gyn) expert testified that the defendants "violated standard of care." As a result, the case was settled on the eve of trial with an agreed contribution by both the ob-gyn and hospital defendants.

2. Renal Embryotoxicity Following ARB Inhibitor in a Pregnant Woman

Valsartan was prescribed for hypertension in a 30-year-old woman and was filled at an outpatient/community pharmacy. The drug was prescribed by a general practitioner physician. A prescription for pre-natal vitamins was on the patient's pharmacy profile, but the pharmacist did not inquire about the patient's pregnancy or warn her about the use of valsartan during pregnancy. The physician learned about the prescription late in the preg-

nancy and the drug was discontinued. However, oligoamnios was viewed on an ultrasound examination by that time.

Fetal urine production is the major source of amniotic fluid (AF) production in the second and third trimesters. If blood pressure drops, angiotensin II maintains kidney perfusion and thus glomerular filtration rate (GFR) due to autoregulation. The use of angiotensin-converting enzyme inhibitors (ACE-Is) and angiotensin II receptor blockers (ARBs) late in pregnancy may cause severe oligohydramnios due to fetal renal impairment in the second and third trimesters. A boxed warning indicates that ACE-Is and ARBs may cause fetal and neonatal morbidity and mortality if used during pregnancy. ACE inhibitors also may increase the risk of major congenital malformations when administered during the first trimester of pregnancy.

Fortunately, the neonate recovered without long-term renal toxicity. The pharmacist claimed he doesn't inquire about pregnancy so as not to embarrass patients and that pre-natal vitamins are "used for other things."

The pharmacist was sued for violation of standard of care. Eventually, it was determined that he should have inquired about the pregnancy and advised both physicians of the ARB prescription. This case was settled by the pharmacy out of court.

3. Deformed Skull in Newborn Following Opiate Therapy During Pregnancy

A claim stated that the mother's use of opiates caused her fetus to experience decreased movement and was the cause of his skull deformity. There were reports that the mother experienced severe chronic pain and that her doctors knew about her opiate use. A lawsuit against the obstetrician was filed.

There are multiple causes of deformed craniums identified in the literature and in antiquity, and even some post-partum cases of floppy babies due to inactivity in the crib. There was no literature support for opiate-induced in-utero flaccidity or for decreased movement causing cranial deformity.

The plaintiff's case was dismissed after the defense pharmacologist's report revealed a lack of clear causation for the claimed injury.

4. "Off-Label" Tocolytics and Beta-Blockers in Hypertensive Premature Labor Resulting in Fetal Loss

The plaintiff was 33 weeks pregnant with uterine contractions and a blood pressure (BP) reading of 149/92; she was admitted for tocolysis. Antihypertensive agents (including the calcium channel blocker, nifedipine) and a tocolytic (terbutaline) were prescribed. Her BP was controlled, the contractions stopped, and the patient was discharged from the hospital. Eight days later she was found unresponsive at home with a suspected eclamptic seizure. An ultrasound in the hospital showed fetal demise (in both twins) along with a placental abruption. The mother continued hemorrhaging and required a hysterectomy.

According to a plaintiff ob-gyn expert, the twins should have been delivered earlier, and if they had been, no adverse outcome would be expected. The maternal fetal medicine (MFM) physician "should have discontinued the anti-hypertensives to get true pressure readings." Nifedipine, the expert commented, "is known to mask hypertension; therefore, the standard of care required the doctor to get true blood pressure readings."

There was conflicting literature as to a direct cause.¹²⁻¹⁵

When a pregnant patient is treated with an antihypertensive agent, it does not mask hypertension—it treats hypertension by lowering BP and thus eliminates or controls hypertension. The defense expert stated that, "Under the circumstances, as a pharmacologist, the use of nifedipine in this case is completely appropriate, the best drug choice for treatment." As a result, the MFM physician and hospital refused to settle. Prior to trial, the parties agreed upon a nuisance settlement.

5. False-Positive Morphine Meconium in Neonate Resulting in Action By Child Protective Services

This case concerned an admitted heroin user, who claimed she had last used heroin in her first trimester, when she learned that she was pregnant. Her obstetrician continued the use of Xanax (alprazolam) to lessen her likelihood of using heroin. The patient used alprazolam throughout her labor and after delivery. The baby's meconium tested positive for morphine (in a screening test),

and it was confirmed with gas chromatography–mass spectrometry testing. No benzodiazepines were detected in the meconium.

The pharmacokinetics of meconium drug disposition and detectability became a key issue in this case. The estimated time of drug use detected in amniotic fluid was eight weeks, and the timing of meconium formation was 12 weeks. Thus, the appearance of drugs (morphine) in the meconium took approximately 20 weeks to detect.

Were the toxicology results accurate? Morphine (from heroin) was present; there had been a long interval from the patient's last use to birth, but it was possible. No benzodiazepines (alprazolam) were detected but they should have been present. Something was wrong with this picture! A pharmacologist expert testifying on the mother's behalf provided an opinion, saying that the "sample must be from another patient." As hospitals do not routinely document the chain of custody in the manner seen in criminal cases, there was no way to verify the chain of custody in this case. With the patient's continuous use of benzodiazepines, the meconium test should have been positive for benzodiazepines. Because the test was negative, it created significant doubt as to the chain of custody of the meconium tested at the confirmation level (the court ruled that the "test cannot be accurate"). Incidentally, the brochure describing the test (ARUP labs) stated: "Not for forensic purposes" (<https://www.aruplab.com/>).

The child protective agency dropped the action against the mother as a result of the questionable identity of the meconium morphine-positive test.

6. Negligent Epidural Infusion of Magnesium Sulfate in a Laboring Woman

Magnesium sulfate ($MgSO_4$) is the agent most commonly used for the treatment of eclampsia and prophylaxis of eclampsia in patients with severe pre-eclampsia. It is usually given by the intramuscular or intravenous route. A concentration of 1.8 to 3.0 mmol/L has been suggested for eclamptic convulsions.

What happens with epidural administration? In this case, a nursing student obtained $MgSO_4$ instead of lidocaine from a Pyxis (drug storage cabinet), and connected the $MgSO_4$ to an epidural cath-

eter. The patient complained of increased pain, burning, and paralysis of her lower extremities, and an examination led to the discovery of a medication error. She was monitored for several days, and fortunately made a full recovery with no residual effects. The newborn was examined and monitored and found to have no signs of magnesium toxicity or elevated magnesium serum levels.

Both the obstetrical and the anesthesia literature is replete with reports of magnesium-administration errors occurring during labor.¹⁶

The hospital, which was sued, blamed the nursing school for inadequate supervision of its student. The plaintiff's pharmacist expert criticized the ease of access to the $MgSO_4$, the lack of supervision of the nursing student, and the verification of the $MgSO_4$ fluid connection.

In this case, the hospital paid a settlement for pain and suffering.

7. Opiate Toxicity and Maternal Death In an Unmonitored Woman in Labor

Post Caesarian-section, a patient received a fentanyl epidural. Her history included the use of antipsychotics, anxiolytics, and antihistamines. Her lung findings showed bilateral wheezing, and she was also morbidly obese. Her pre-operative drugs were re-ordered and administered post-partum to help relieve post-partum depression.

No pulse oximetry was used by the labor and delivery nurses post-partum, although it is well known that opiates cause respiratory depression at therapeutic doses. Central nervous system depressants add to opiates' respiratory depressant effect. Sleep apnea, morbid obesity, respiratory compromise, and abdominal surgery increase the risk of opiate respiratory depression. The only effective means of monitoring is by the frequent checking of vital signs and pulse oximetry and/or capnography.

The patient experienced cardiac arrest 16 hours post-op. She was resuscitated, but developed hypoxic encephalopathy and permanent brain damage.

The hospital had a pulse oximetry policy in place, and the anesthesiologist had ordered pulse oximetry for this patient. Inexplicably, the labor and delivery nurses testified that "We don't use pulse ox in Labor and Delivery."

The case was tried by a jury, resulting in a \$16 million verdict against the hospital. The hospital subsequently negotiated an \$8 million cash settlement, which was accepted by the family to avoid appeal.¹⁷

DISCUSSION AND P&T COMMITTEE IMPLICATIONS

All of these cases represent an adverse pharmacologic event that in some way harmed a patient. The type of harm and cause varied, but all involved commonly used drugs used within a complex case in which negligence by one or more care providers occurred.

P&T committees have a long history with legal responsibilities that have been set forth by the judicial system; the question is, how do committees ensure that their core duties are executed within their increasingly expanding and/or complex organizations. Not only are fundamental societal agencies like courts and regulatory bodies looking closely at health care providers and organizations, consumers and other non-health-care stakeholders are also questioning the practices and activities occurring or not occurring within the health care system. As these drug-related health care delivery cases illustrate, there is a need to step back and rethink how best to ensure that a health system's fundamentals of care and safety remain the highest priority. In a typical health care entity, this would require several committees engaging in and collaborating on not merely improving outcomes but ensuring the quality and safety of care. This emphasis on basic monitoring and improved performance has been the focus of employer-driven groups like Leapfrog, Amazon–Berkshire–JPMorgan Chase, and Catalyst for Payment Reform.

Committees that support medical staff in hospitals and health care organizations have always encountered resource shortages, among other challenges. In these times of change, providing more infrastructure and resources that support key committees such as P&T would be prudent as part of a robust risk-management strategy.

CONCLUSION

Given the inherent complexity of obstetrics and reproductive medicine, it is interesting to note that the medication-related injuries leading to the most litigation involve some of the most com-

monly used drugs in therapy—some of them generations old—and not the newer, more complex therapies. These cases also serve as a poignant reminder that highly sophisticated treatment of a high-risk pregnancy can be jeopardized by a simple negligent act committed by caregivers or by patients.

Amid the endless changes in the health care sector, there remains little question that the importance of P&T committees will continue even as their specific roles and responsibilities shift depending on the demands of the individual organization or insurance program. Violations of regulatory and reimbursement rules are likely to increase the costs associated with drug use and dispensing. And the inadvertent failures among health care professionals and providers, together with supply chain deviations from approved policies, will continue to result in drug injury and subsequent exposure to litigation risk, including malpractice. Along with the rise in consumerism in a progressively litigious society, we can expect an increase in drug-related litigation in the U.S.

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