A 42-year-old woman named L.M. was diagnosed with recurrent papillary serous ovarian cancer. Following 12 weeks of treatment with the chemotherapeutic agent doxorubicin hydrochloride (HCl) liposome injection, she received notification from her healthcare provider that the U.S. Food and Drug Administration (FDA) announced that the drug was unavailable because of manufacturing issues. L.M.’s healthcare provider informed her that her chemotherapy protocol would need to be altered midtreatment. She, like other patients with cancer, would be offered a different treatment regimen that potentially had increased side effects and was less effective. L.M. followed recommendations to begin an alternative treatment regimen. Unfortunately, after three treatments with the alternative regimen, L.M.’s CA-125 level increased and a computed tomography scan of her abdomen and pelvis demonstrated disease progression. L.M.’s story exemplifies a common finding in the multidimensional impact of the pharmaceutical drug shortage, and the analysis shows patients who are most burdened by drug shortages and have experienced substandard care, increased cost of care, and compromised quality of health care.
Overview of Drug Shortage

A drug shortage occurs when the total supply of all clinically interchangeable versions of an FDA-regulated drug fails to meet the current or projected demand for the estimated patient demand level (Alspach, 2012; Carter, 2011; Golembiewski, 2012). Drug shortages in the United States began in the 1990s, but the problem continues to worsen with time. When an inadequate supply of a drug exists, pharmacies alter how they stock and order medications, which directly affects patient access to necessary treatments. A survey of hospital pharmacies demonstrated unnecessary waste of pharmaceuticals that were in short supply because of drug manufacturers’ shelf-life recommendations. Those outdated requirements on shelf life from the Centers for Medicare and Medicaid Services (CMS) are contradicted by evidence-based literature (Golembiewski, 2012; Mayer, 2012).

According to the FDA (2013), the United States is plagued with record numbers of pharmaceutical shortages, particularly those involving sterile injectable drugs (e.g., chemotherapy agents, anesthetics), causing a national public health crisis and limiting access to cancer care (Gatesman & Smith, 2011). In five years, the number of drugs in short supply has tripled from 61 pharmaceutical agents in 2005 to 178 in 2010. Of those, 132 included sterile injectable agents. Those numbers continue to rise with 251 drugs reported in 2012, 183 of which involved sterile injectable agents. Many of those agents are used in the standard treatment of many oncology protocols for childhood, breast, hematologic, and gynecologic malignancies (FDA, 2013) (see Table 1). The shortage of chemotherapy agents creates a huge burden. Patients with cancer who are undergoing treatment cannot be switched to another chemotherapy agent without repercussions. Equivalent dosing for substitute regimens often is absent, and substitutions are not based on evidence gathered from previous randomized clinical trials.

The American Hospital Association reported that 99.5% of hospitals experienced pharmaceutical drug shortages (Gatesman & Smith, 2011). In addition, the American Society of Health System Pharmacists reported that drug shortages are at the highest level in more than a decade and that the shortages are by far the worst in 30 years (Gatesman & Smith, 2011). The most commonly reported pharmaceutical shortages are injectable and infusion agents, antibiotics, and chemotherapy agents (Larkin, 2011).

Medication Errors

Another adverse health outcome from drug shortages is medication error. Larkin (2011) attributed at least 15 deaths to pharmaceutical drug shortages during a 15-month period, which included a case where sepsis resulted from tap water being substituted for sterile water when flushing feeding tubes prior to and after medication administration. Other deaths occurred when medications were substituted during intubation and the patients developed fatal laryngospasms. In addition, patients suffered chemotherapy complications or fatal side-effect toxicities when delays or cancellations in treatment or drug substitutions were instituted because of the shortages of chemotherapy agents (Alspach, 2012; Gatesman & Smith, 2011; Jensen & Rappaport, 2010; Larkin, 2011).

To capture the danger of these shortages, the Institute for Safe Medication Practices is attempting to track near misses of medication errors from drug shortages (Larkin, 2011). From July to September 2010, data revealed that 35% of healthcare providers reported a near miss of a medication error, and 25% of clinicians reported that medication errors occurred while attempting to substitute or replace a drug as a result of a drug shortage (Alspach, 2012; Beeson, Lehrfeld, Fowler, & Manifold, 2012; Doyle, 2011; Gatesman & Smith, 2011). Clinicians also have noted that, of the errors reported, inexperience with replacement pharmaceuticals was cited as the most common reason for medication errors (Gatesman & Smith, 2011). Alspach (2012) reported in an analysis of 228 hospital and pharmacy professionals that 80% of those evaluated had experienced pharmaceutical shortages that led to patient treatment delays or cancellations. Chabner (2011) cited that the risk of medication error increased with the use of substitutions in alternative treatment regimens. For example, Chabner (2011) reported that patient safety was compromised when chemotherapy agents were substituted or replaced and

<table>
<thead>
<tr>
<th>Drug</th>
<th>Use for Drug</th>
<th>Reason for Shortage</th>
<th>Date of Last Noted Shortage</th>
</tr>
</thead>
<tbody>
<tr>
<td>Daunorubicin hydrochloride</td>
<td>Chemotherapy agent</td>
<td>Increased drug demand; manufacturer shortage</td>
<td>August 20, 2013</td>
</tr>
<tr>
<td>Doxorubicin hydrochloride liposome injection</td>
<td>Chemotherapeutic agent; primary and secondary treatment of reproductive cancers</td>
<td>Manufacturer shortage (Sun Pharma Global FZE); solved by a temporary importation of Lipodox (doxorubicin hydrochloride liposome injection)</td>
<td>April 10, 2012</td>
</tr>
<tr>
<td>Doxorubicin lyophilized powder</td>
<td>Chemotherapeutic agent</td>
<td>Discontinuation of drug production</td>
<td>April 10, 2012</td>
</tr>
<tr>
<td>Leucovorin (calcium lyophilized powder for injection)</td>
<td>Folic acid analog; used in conjunction with methotrexate; high risk of dosing error with substitute (levoleucovorin)</td>
<td>Drug manufacturer discontinuation (Bedford Laboratories); regulatory delay (Teva Pharmaceuticals, APP Pharmaceuticals, and Sagent Pharmaceuticals)</td>
<td>August 20, 2013</td>
</tr>
<tr>
<td>Vinblastine sulfate</td>
<td>Chemotherapy agent</td>
<td>Increased drug demand</td>
<td>December 7, 2012</td>
</tr>
</tbody>
</table>

Note. Based on information from U.S. Food and Drug Administration, 2013.
when dosing regimens were altered with substitute pharmaceuticals to meet replacement drug protocols. Standardized treatment guidelines evolve from randomized, controlled trials that evidence the best health outcomes for various malignancies. Once the treatment is altered in any way from the regimen tested in the trial, the patient no longer receives evidence-based treatment. When healthcare providers are forced to select alternative chemotherapeutic agents because of unforeseen shortages and choose alternative protocols based on availability rather than evidence, patient safety and care are compromised, which creates substantial ethical and legal issues as well as risk for future refinement of cancer treatment (Chabner, 2011; Gatesman & Smith, 2011; Link, Hagerty, & Kantarjian, 2012).

Drug Shortage Etiology

Since 2005, manufacturers discontinued production of many drugs for reasons that included pharmaceutical mergers, limited profit margins, increased cost of pharmaceutical drug manufacturing, shortages of raw materials for drug development, contamination of raw materials for drug development, increased pharmaceutical drug demand, increased regulatory processes that delay drug manufacturing, and the use of older manufacturing plants that are less efficient for drug development (Carter, 2011; Gehrett, 2012; Golembiewski, 2012; Holcombe, 2012; Mayer, 2012). The high cost of production for many of the chemotherapy agents may make it nearly impossible for community and hospital pharmacies to keep a sufficient supply on hand when a steep financial risk exists of discarding the drugs if they expire before they are used.

Limited Profit Margins

To keep the cost of chemotherapy drugs low for third-party payers (e.g., insurance companies) and to eliminate incentives for overuse because of high profit margins, drug profit margins have been severely reduced since 2005 when legislation changed Medicare’s pricing policies (Gehrett, 2012; Holcombe, 2012). With low fixed reimbursements from third-party payers such as Medicare, a pharmaceutical company’s ability to manufacture drugs is challenging. Limited profit margins prohibit pharmaceutical companies from making vast profits when drugs move off patent and become generic and less profitable to develop and distribute. When a pharmaceutical drug is available as a generic, the net profit margin for the company is limited, and often the company is not interested in manufacturing the drug. In addition, fixed Medicare legislation and increased drug demand have caused many companies to seek cost-containment measures (Golembiewski, 2012). Once cost-containment measures take effect, companies use older, less efficient manufacturing facilities; use less expensive raw materials for drug development; and decrease the employee base (Chabner, 2011; Gehrett, 2012). Several pharmaceutical companies (e.g., Bedford Laboratories, Hospira) have experienced issues (e.g., contamination of drug vials, manufacturing delays) because of cost-containment measures (Alspach, 2012; Gatesman & Smith, 2011; Larkin, 2011). Teva Pharmaceuticals, one of the largest generic-producing pharmaceutical companies, has experienced drug shortages as a result of limited resources of raw materials to manufacture drugs, microbial contamination during drug development, and an increase in drug demand (Gatesman & Smith, 2011).

Gray Market Systems

Pharmaceutical drug shortages also have produced a secondary gray market, a system where middlemen from nontraditional manufacturers sell pharmaceuticals that are in short supply at premium prices (Larkin, 2011). Gray market concerns include pharmaceutical drug safety, interruption in the pharmaceutical supply chain to hospitals and pharmacies, lack of reputable distributors, and the legal and ethical issues of paying inflated prices to middlemen (Larkin, 2011).

Legislative Mandate

Reimbursement for pharmaceuticals has decreased significantly since the Medicare Prescription Drug, Improvement, and Modernization Act (enacted in 2003 and implemented in 2005) substantially reduced payment rates for chemotherapy drugs and other high-cost injectable and infusion agents (Gehrett, 2012; Jacobson, Earle, Price, & Newhouse, 2010; Kaakke et al., 2011). The Medicare Modernization Act set the chemotherapeutic drug agent reimbursement restriction to a maximum of a 6% markup. Prior to this act, oncology practices purchased chemotherapy drugs at 66%–88% of the average wholesale price and were reimbursed at 95%, which resulted in a profit margin large enough to cover the cost of the chemotherapy nurse, chemotherapy administration, and practice cost for office administration. Medicare currently reimburses physician practices and healthcare systems for the average sales price (ASP) for the drug, which covers the cost of the drug itself plus a 6% markup (CMS, 2013; Jacobson et al., 2010; Mayer, 2012).

Although the Medicare guidelines that limit the pharmaceutical markup to 6% of the ASP may seem reasonable, the reduction in the reimbursement for healthcare systems and private independent healthcare providers fails to allow a profit margin for the maintenance of professional staff and facilities to deliver the drug safely and efficiently (Jacobson et al., 2010). If healthcare providers are not reimbursed adequately to maintain the staff and facilities needed to deliver the drug, they are unable to afford to sustain administration (Havrilesky, Garfeld, Barnett, & Cohn, 2012; Jacobson et al., 2010). In addition, the drug may cost more than the ASP plus the 6% markup reimbursement for the healthcare provider if, for example, the cost of a pharmaceutical change from the time of administration to the time of reimbursement. Healthcare providers also may pay for the drugs on credit, incurring interest charges that could exceed the allowable 6% profit margin. Many healthcare systems and private providers purchase the pharmaceutical agent and are not reimbursed by Medicare or third-party payers for 3–6 months after drug administration. The delay, suspension, or absence of adequate reimbursement for pharmaceutical purchases poses significant financial risk to healthcare institutions, burdening the provider and institution (Havrilesky et al., 2012; Jacobson et al., 2010). As pharmaceutical costs rise for specific agents because of shortages of generic pharmaceuticals that are less expensive, healthcare providers and facilities may not be able to sustain the financial risk of purchasing and administering a more expensive agent, which would increase generic drug demand. Although the priority of healthcare systems and providers is to deliver consistent, high-quality evidence-based care,
the cost of purchasing and delivering this level of care must be balanced with reimbursement to maintain sustainable, high-quality service (Havrilesky et al., 2012; Jacobson et al., 2010).

Impact of Drug Shortages on Patient Care

Traditionally, healthcare providers have relied on pharmaceutical agents to treat patients under the guidelines and recommendations of evidence-based standards of care regulated by the FDA (Burr, 2012). Inadequate and inconsistent drug supply has altered clinical care. Depending on pharmaceutical availability, patients may not be treated based on evidence-based practice, which has affected patient care (Alspach, 2012; Burr, 2012; Gatesman & Smith, 2011; Larkin, 2011). The lack of authority and autonomy of healthcare providers to render evidence-based care has delayed treatments and increased unanticipated side effects or toxicities, medication errors, and healthcare costs for patients and providers (Gatesman & Smith, 2011).

Ethical and Legal Issues of Drug Shortages

Ezekiel Emanuel, MSC, MD, PhD, oncologist and professor of medical ethics and health policy at the University of Pennsylvania, stated, “Most shortages appear instead to be the consequence of corporate decisions to cease production, or interruptions in productions, caused by money or quality problems, which manufacturers do not appear to be in a rush to fix” (Emanuel, 2011, para. 5). Drug shortages are caused, in part, by manufacturers’ preference to produce more profitable brand-name drugs rather than generics that do not generate as much profit.

Although the FDA does not dispute that significant ethical and legal implications are present in widespread pharmaceutical shortages, much of the argument lies in the hands of the pharmaceutical industry. Pharmaceutical companies have an ethical and legal responsibility to safely manufacture and distribute pharmaceuticals to patients, providers, and healthcare systems. Pharmaceutical companies argue that they are able to determine drug cost based on profit margin, cost of raw materials, and cost of maintaining drug development facilities and personnel for research and distribution, and they must maintain sufficient profit margin to sustain manufacturing and distribution (Havrilesky et al., 2012; Thompson, 2009).

Healthcare providers contend that delivery of care is influenced by profit margins of those pharmaceutical companies and third-party payers who decide drug cost and reimbursement. Many patients have received second- and third-line pharmaceuticals, have experienced treatment protocol interruptions with delays and cancellations, and have experienced unnecessary side effects and toxicities from substitute or alternative drug protocols, all of which affected the quality of their care (Thompson, 2009).

Since 2008, obtaining leucovorin, a drug used to prevent harmful effects of methotrexate, has posed a challenge for healthcare providers (Kaakeh et al., 2011). The National Cancer Institute sent instructions to cancer centers on how to address the national shortage. Although pharmacists did not admit to stockpiling the drugs, many ordered large quantities when they received notice that their manufacturers were in short supply. The American Society of Health System Pharmacists has advised healthcare organizations to refrain from stockpiling drug products since 2001 because of the risk of increasing cost to healthcare organizations (Kaakeh et al., 2011). Physicians, pharmacists, and healthcare administrators argue that planning is essential when considering patient needs. Establishing committees for deciding which patients take priority when drug shortages occur and communicating with patients and providers on distribution and administration of drugs would ease confusion and prevent the urge to stockpile. Figure 1 shows a sample action plan for drug shortages.

Until healthcare providers and pharmaceutical companies agree on a systematic process of how to handle a drug shortage when it occurs, they are left to decide how best to protect their own interests, sometimes to the detriment of patient safety and quality of care. Healthcare providers argue that stockpiling may be more effective and ethical because, ultimately, patient safety and providing quality care to patients are compromised during a shortage. Although research for future drug treatment protocols is important, issues at the point of care take precedence for healthcare providers.

Interventions to Decrease Drug Shortages

After Congress began to address pharmaceutical drug shortages, the FDA was responsible for regulating drug safety and preventing and resolving drug shortages, particularly those drugs that are medically necessary (Alspach, 2012). When pharmaceutical companies experience manufacturing and quality issues, the FDA must work closely with the company for swift resolutions preventing and resolving drug shortages, particularly those drugs that are medically necessary (Alspach, 2012). When pharmaceutical companies experience manufacturing and quality issues, the FDA must work closely with the company for swift resolutions to prevent patient harm (FDA, 2011, 2013). In addition, the FDA is responsible for monitoring drug production to help avert drug shortages. When the American Society of Clinical Oncology (2011) realized the scope of the national drug shortage, they hosted a summit to address the issue. In response, the FDA’s Cen-
Implications for Practice

Nurses should take leadership roles in the development and implementation of policies and procedures at the point of care to address drug shortages in healthcare institutions. Nurses play an important role in education, patient advocacy, and policy development to address issues surrounding drug shortages and their impact on patient care.

Conclusions

Access to evidence-based care for patients with malignant diseases depends on the availability of necessary pharmaceutical agents. The drug shortages create difficulties for patients as well as the healthcare team caring for them. The issue of drug shortages is multifaceted, and it affects all aspects of health care from patients, caregivers, and healthcare providers to third-party payers, the pharmaceutical industry, and regulators. Drug shortages have grown significantly since 2000, increasing healthcare costs and compromising patient care. Nurses are important members of the healthcare team who have the opportunity to assist in patient advocacy efforts to address the issue of drug shortages.

References


Implications for Practice

- All healthcare providers must work together to identify and manage the shortage and its potential impact to patient care outcomes.
- Nurses should take leadership roles in the development and implementation of policies and procedures at the point of care to address drug shortages in healthcare institutions.
- Nurses play an important role in education, patient advocacy, and policy development to address issues surrounding drug shortages and their impact on patient care.


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