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Keep Your Guard Up: The Potential Impact of Drug Shortages on Pharmacoepidemiological Studies

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1 | Introduction

Drug shortages continue to affect healthcare systems worldwide and compromise patient care. The US Food and Drug Administration defines a drug shortage as a situation where the demand for a drug exceeds the supply [1]. In the first quarter of 2024, the US experienced a record high of 323 active drug shortages, the most since 2001 [2]. The current number of drugs facing shortages in two or more countries has increased by 101% from September 2021 [3]. Nearly all drug classes and formulations are affected by shortages [2]. Drug shortages can manifest as temporary delays in drug availability or even permanent drug discontinuations [4]. Disruptions in drug supply and access can cause treatment alteration or discontinuation at the patient level, leading to missed or delayed treatment, medication errors, increased healthcare costs, and even mortality [5, 6].

Drug shortages can alter patient drug access and prevent utilization. Shortages can lead to decreases in utilization anywhere from 1%–99% for different drug shortages [7]. Conversely, the same shortage event can have varying impacts on use between countries. The 2018 valsartan recall caused a global decrease in use by 15.7% and changes in usage within countries ranging from 1.2% decreases to 25.0% increases [8]. This highlights how a single shortage event can differentially affect countries. However, not all shortages lead to changes in drug utilization, since some events can be mitigated given supply chain resilience, alternative therapy options, and policy measures [4]. In most situations, a drug shortage can result in switching to alternative treatment options. Such shifts in patient drug use can translate to larger shifts at the population level and dramatically alter utilization patterns of many other drugs and drug classes. These significant shifts and biases in drug utilization patterns, if unaccounted for, may impact the validity and reliability of pharmacoepidemiology studies. This paper will highlight important cautions regarding the potential implications across study types and discuss how addressing these challenges can transform how future studies are conducted.

2 | Drug Utilization Research

If researchers are not aware of both historical and current drug shortages, inaccurate conclusions may be drawn when conducting drug utilization studies. During shortages, healthcare providers may need to substitute a shortage drug with an alternative. These switches may not always be a perfect substitution regarding therapeutic equivalence, dosage, formulation or 'on-label' use. Medication switching due to drug shortages can create an artificial shift in drug utilization studies, making it difficult to determine true drug therapy switches in clinical practice. Drug utilization studies may also find unusual prescription patterns caused by anticipatory stockpiling. This can lead to spikes in medication use followed by rapid declines when the stock has been exhausted, making it difficult to differentiate between shortage-induced fluctuations and real-life changes. Artificial spikes in drug use might also be caused by delayed treatment initiations due to shortages, leading to temporary declines in use, followed by spikes. Importantly, not all shortages lead to dramatic drops in drug supply. Thus, smaller

Summary

- Drug shortages have become more common and continue to hinder patient care.
- Shortages can alter patient drug access, causing shifts in drug utilization patterns and impacting the validity and reliability of pharmacoepidemiology studies.
- Shortages can lead to abrupt fluctuations in usage trends due to medication switches and can affect measures of adherence and persistence.
- Researchers need to consider the impact of drug shortages when designing pharmacoepidemiologic studies to avoid biases.
- Accounting for shortages in research calls for different strategies, such as consulting drug shortage reports and conducting preliminary drug use studies to detect abnormal patterns.

shifts may not be as easily recognizable. Researchers must account for supply-related disruptions when analyzing findings and considering their implications for healthcare policy decisionmakers and clinical practice. A recent study analyzed prescribing patterns of folic acid in pregnant women taking antiseizure medication for epilepsy between 2006 and 2017 in Denmark [9]. There was a folic acid shortage in 2006 resulting in no drug sales for the year 2006 [10]. Researchers navigated this problem by omitting folic acid utilization data for years 2006–2009.

3 | Adherence and Persistence Studies

Drug shortages can also affect studies of adherence and persistence. Adherence is the extent to which a patient takes a medication as prescribed in terms of dose, timing, and frequency [11, 12]. The most common measures of adherence are the medication possession ratio (MPR) and the proportion of days covered (PDC). The MPR is calculated as the number of days of medication supply within a specified observation period (numerator) divided by the number of days in that period (denominator). When calculating the PDC, the numerator is the number of days in the observation period that were covered by the medication [12, 13]. If a medication becomes unavailable, the patient will redeem fewer prescriptions than usual during the observation period, thereby causing the numerator to decrease and the adherence to be underestimated. Persistence refers to the continued use of a prescribed medication over time [11, 12, 14]. Kaplan–Meier survival analysis and the proportion of patients covered (PPC) are common methods to measure persistence. The Kaplan–Meier survival curve shows the proportion of persistent patients over time. A patient is considered to have discontinued treatment and thus be non-persistent if the patient fails to refill a prescription within a predefined "grace period" after the end of the last prescription's days of supply [12, 14]. During a drug shortage, missing prescription refills may therefore result in a decreased persistence at any given time after treatment initiation and thus a faster declining Kaplan–Meier survival curve. The PPC method measures persistence as the proportion of living patients who are covered by a prescription at any given time after treatment initiation. If a patient is unable to redeem prescriptions for a medication during a shortage period, the patient is no longer covered by treatment and therefore excluded from the numerator. If the medication becomes available again, and the patient redeems a prescription, the patient reenters the numerator [12, 14]. Therefore, the underestimation of persistence is expected to be less marked than in a Kaplan–Meier survival analysis and a plot of the PPC by treatment over time to show a less steep decline.

4 | Drug Safety and Effectiveness Studies

Drug shortages can introduce bias in studies of associations between drugs and outcomes leveraging data on filled prescriptions to define either exposure and/or outcome. In cohort studies using an "intention-to-treat" approach, patients are analyzed according to their initial exposure status, irrespective of any changes in exposure status during follow-up [15]. If an exposure drug becomes unavailable during follow-up due to a shortage, and patients switch to alternative drugs or remain untreated, they would still be classified as exposed users, despite actually being nonusers. Since it is unlikely that the exposure groups would experience drug shortages to the same extent during follow-up, the degree of exposure misclassification would most likely differ between the groups. This could lead to bias in both directions, either under- or overestimating the true effect. Conversely, when using an "as-treated" approach, a drug shortage would result in patients being censored at treatment discontinuation, typically defined as no refill of the exposure drug within the days' supply of the last fill plus a grace period [15]. This would result in lost follow-up time for patients who resume treatment when the exposure drug becomes available again. If the patients are followed for several years, and an exposure drug becomes unavailable for a few months, the information loss resulting from stopping the patients' entire follow-up in an as-treated analysis may be more problematic than the few months of exposure misclassification in an intention-to-treat analysis. Drug shortages can also affect the estimation of propensity scores used to control for confounding in cohort studies. The propensity score is an estimate of the probability that a patient receives one treatment over another, given a set of baseline characteristics, or covariates [16]. These covariates may behave unexpectedly during a drug shortage period. For example, if patients over 60 years are recommended drug A, and age is included as a covariate in the propensity score model, then age over 60 becomes a strong predictor of receiving drug A. However, if there is a shortage of drug A for a certain period, and the patients end up receiving drug B instead, then age over 60 will no longer predict the choice of drug A over drug B, but rather point toward drug B due to the absence of drug A. Calendar year adjustment may be even more challenging. If calendar year is included as a covariate in the propensity score model, and drug A becomes unavailable in a specific year, the model may predict that patients are more likely to receive drug B in that year.

5 | Recommendations

Here, we provide suggestions on handling drug shortages when conducting research. First, a basic drug utilization study prior

to analysis could serve as a reference for detecting deviations caused by shortages. Second, consulting medical agencies, data registries, or local reports on shortages might provide current and historical information on shortages with potential implications for clinical practice. Many organizations across the world have developed drug shortage reporting websites including Health Canada, the US Food and Drug Administration, the American Society of Health-System Pharmacists, and the European Medicines Agency [17–20]. Third, consulting a drug specialist or pharmacist with expertise in certain drug groups about shortages within the given area may offer valuable insights into potential alternative courses and clinical prescribing behaviors during shortages. Such collaboration will help ensure a comprehensive understanding of different nuances associated with specific drug shortages. Fourth, since healthcare providers substitute drugs or adjust treatment regimens, shortages inadvertently create natural experiments for real-world observation. Utilizing these observations within the framework of pharmacoepidemiological outcome studies, we as researchers can gain otherwise unobtainable insight into drug effectiveness, safety and patient outcomes associated with alternative drug switches and therapies. In 2012–2013, Norway withdrew digitoxin from the market, requiring all patients to switch to digoxin. Digitoxin has been linked to a higher risk of diabetes [21], making this discontinuation a natural experiment to determine whether the increased risk is specific to digitoxin or a general effect of its drug class. Accounting for the impact of drug shortages when conducting research may call for different strategies. However, by considering basic study methods, data from registries and local data, expert consultations, and adaptive strategies, we can navigate the difficult challenges that drug shortages pose for drug utilization studies.

Conflicts of Interest

The authors declare no conflicts of interest.

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