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Adverse Event Detection & Reporting: What Healthcare Providers Need to Know

Announcer:
Welcome to ReachMD.
This medical industry feature, titled “Adverse Event Detection and Reporting: What Healthcare Providers Need to Know” is sponsored by Amgen.

Here’s your host, Dr. Matt Birnholz.

Dr. Birnholz:
Did you know that approximately one half of all safety-related changes made to a drug’s label are based on post-approval adverse event reports?[1] This week we will be discussing what healthcare providers need to know about adverse event detection and reporting.

This is ReachMD, I’m Dr. Matt Birnholz. Joining me to discuss pharmacovigilance is Dr. Jessica Ailani, Vice Chair of Strategic Planning in the Department of Neurology at Medstar Georgetown University Hospital in Washington, DC.

Dr. Ailani, welcome to the program.

Dr. Ailani:
Thank you so much for having me.

Dr. Birnholz:
So, Dr. Ailani what exactly *is* pharmacovigilance and why is it important? Why do clinicians need to care about it?

Dr. Ailani:
Those are great questions, ones that physicians may not think about. So, pharmacovigilance is really an umbrella term for all activities related to detection, assessment, understanding, and prevention of drug-related adverse effects and any other possible drug-related problems.[2] These adverse events are generally detected in two stages—first, during clinical trials, and second, when the drug is being used in the real-world. In clinical trials, adverse events are monitored throughout the duration of the study, and across all phases of the study, but safety monitoring of trials is by nature, is finite.[3-5] In contrast, real-world adverse events are monitored for the entire time the drug is available to the public—which can be an indefinite amount of time.[6-8] Because healthcare providers not only prescribe medications, but are involved in treating any adverse events that arise, clinicians play an essential role in pharmacovigilance.[9] As a result, healthcare providers should officially report events to the United States Food and Drug Administration or the FDA, or to the drug manufacturer, or to the local adverse event drug reaction monitoring body, for example, institutional committee that is responsible for monitoring adverse events.[1,9] Proper clinician reporting of post-marketing drug-related adverse events ultimately improves our understanding of the given medication and can impact the medication’s label and its use.[9]

Dr. Birnholz:
But Dr. Ailani, aren’t the most relevant drug-related adverse events revealed during clinical trials and isn’t that how drugs are deemed safe enough for use in the general population?

Dr. Ailani:
So yes, in one sense they are, but you bring up a really critical point. While clinical trials reveal one set of potential adverse events, use of a drug in the real- world setting may unveil a different set of adverse events. In a real-world setting, the population using the drug may

be very different from the population using the drug in a clinical trial.[8,10,11] In a clinical trial, patients are selected based on pre-specified eligibility criteria.[5,8] However, in the real world setting, the patient population can be heterogenous, may have more comorbidities, and may be receiving additional concomitant medications. [10,11] As a result, the real world setting can show adverse events that either might not have been present in the clinical trial setting, or which appeared at a frequency similar to that seen in the general population, so was considered insignificant. [10,11]

It's also important to note that in a clinical trial, the incidence of adverse events in patients taking the drug is compared to the incidence of the same adverse events in a control group—either a placebo or standard of care population, most commonly. However, in the real-world setting, there is no control group, so many adverse events can be considered potentially drug-related.[4,7,12]

Because different considerations exist between adverse events that are reported in clinical trials and in the real-world setting, *both* inform us about product safety and are necessary.[3,6,7]

Dr. Birnholz:
So how then can we know that an adverse event is truly related to the drug versus a rare symptom of the disease itself?

Dr. Ailani:
That's a really good question. It's essential to remember that observing an adverse event is not the same as attributing causality of that adverse event to the drug. To properly assess causality, a large sample size may be needed. Premarketing studies of drugs, meaning clinical trials, are large enough to detect common adverse events, but they cannot detect all adverse events.[7] For events that often occur spontaneously, like stroke or pulmonary embolisms, continuous and systematic follow-up of the drug's use in the real-world helps to distinguish, as much as possible, true drug-related causality.[10]

Dr. Birnholz:
So it sounds like in the real-world, many factors could contribute to adverse events. But how then do you determine which adverse events are drug-related and which are not? And is that even possible?

Dr. Ailani:
You're exactly right. It's a very complex issue. While many confounding factors in a randomized controlled trial are reasonably identified and minimized as much as possible by the eligibility criteria that I previously mentioned,[5,8] in the real- world setting there may be a multitude of factors, which can make it challenging to establish a causal relationship between the drug and the adverse event.[10] For example, adverse event data that are spontaneously reported to the drug manufacturer may be incomplete or confounded by the existence of other medical conditions or medications that could either be the cause of or a contributing factor to the event in question.[10,13] Similarly, incidence rates of adverse events in the real world include a background rate of occurrence in the general population.[10] Detective work using national health statistics, published medical literature, ad hoc studies, as well as ongoing epidemiological investigations can help us determine which adverse events occur at a higher frequency in people taking the drug than in the general population, and therefore potentially drug-related.[10]

Dr. Birnholz:
For those just tuning in, this is ReachMD and I'm Dr. Matt Birnholz, and here with me today is Dr. Jessica Ailani to talk about the importance of pharmacovigilance.

So Dr. Ailani, let's continue our discussion on adverse advents with a focus on how they're reported. And let's say that I use a medication, I have a bad reaction. What should my doctor do?

Dr. Ailani:
That's a great question. Most people, and even some clinicians, are unaware of this process. So, let's break this down into the two settings- the clinical trial, and the real-world setting. In clinical trials, the sponsor company, who is running the trial, is required to report all adverse events to regulatory agencies regardless of causality, and according to specified timelines.[3,6,7,14,15] In the real-world setting, healthcare providers play a key role in this process.[9] Clinicians are ethically and professionally obliged to report any adverse events their patients inform them about.[9] So if a patient comes to their office with a medical issue following the use of a medication, it is a healthcare provider's responsibility to report the issue as a possible adverse drug reaction.[9] Healthcare providers can report adverse events directly to the FDA through the Medwatch program, using an online form.[9] Physicians also have the option to inform the drug manufacturer of an adverse event, and they can do so by calling the toll free number provided in the package insert for the drug or on the company's website, or by telling the local representative of the company that a suspected adverse reaction has occurred. All drug manufacturers have a regulatory obligation to report adverse events associated with their products to the FDA, even after approval of

the product,[9] just as would happen in a clinical trial.

Finally, many medical institutions have offices or committees designated for adverse event reporting. Hospital pharmacies, for example, often have committees that are tasked with collected reporting of adverse events and forwarding these reports to the FDA. Similarly, patient safety or quality improvement departments often offer the same service to physicians within a practice or medical group.[9] Thus, there are very defined processes for reporting of adverse events, and physicians play a critical role in this process.[16]

Dr. Birnholz:
But clearly, Dr. Ailani, it's not enough just to point out that a possible drug- related adverse event has occurred. So, how can causality of an adverse event be attributed to a drug, and what do drug manufacturers and regulatory agencies do with this information?

Dr. Ailani:
Well now that's a critical question. Once adverse events are reported, they have to be evaluated for drug causality so they can be appropriately managed. This involves screening all adverse events reports across various databases, mining the data to detect new safety signals, and evaluation of the signals for an overall risk- benefit assessment.[2,15] All reported adverse events are documented in centralized databases maintained by drug manufacturer or regulatory authorities, for example the FDA's Federal Adverse Event Reporting System, also referred to as FAERS, or the World Health Organization's VigiBase.[6,10,16] Detection of a safety signal, meaning a new or unknown adverse event that is potentially caused by a medicine that warrants further investigation, is accomplished by statistical analysis of these databases, along with the assessment of spontaneous reports. This can identify serious or previously unknown adverse drug reactions.[10,13,17] Once a possible risk is detected, all available pre-clinical, clinical, post-marketing, and epidemiological data for that drug are then evaluated to perform a risk-benefit analysis, ultimately to determine if a new risk has been identified that needs to be communicated.[10,18]

Dr. Birnholz:
Some great points Dr. Ailani, but as we come to the end of our discussion, my final question to you is how does this process ultimately affect patients, caregivers, and clinicians?

Dr. Ailani:
Well ultimately, regulatory authorities like the FDA make the final decision on what actions should be taken if a new risk is identified. In the pre-approval setting, this can include changes to clinical trial documents including study protocols and informed consent documentation.[2,15] In the post-approval setting, safety signals found to be linked to risk may lead to variety of changes in how the drug is used or regulated. The newly identified risk may lead to a product label update, dispensing of the drug by specialized pharmacies or physicians, may require monitoring of the patients who uses the product, or may force the drug to be withdrawn from the market completely if the benefit-risk profile is no longer favorable.[11,15,18] Changes are made to the drug's label based upon careful evaluation of the risk to benefit ratio of such changes. The regulatory agency must balance the potential risk posed by the drug against the magnitude and nature of this established clinical benefit, and the uniqueness of those benefits.[10] For example, are there alternate treatments for the disease with similar benefits without equal risk? What is the severity of the disease the drug is used to being, to treat? Does this change the overall risk-benefit profile of the drug? More specifically related to how these changes affect clinicians and patients is the method by which updated clinical use information is disseminated. Methods include "dear healthcare provider" letters, patient leaflets, advertising campaigns directed to health professionals or directly to consumers, scientific journal publications targeting providers and lay press publications targeting consumers, as well as educational programs provided via print, video, audio, or computer media for both audiences to make them aware of the changes.[18] Physicians and patients are thus made aware of any changes in medication use recommended by the regulatory authority. Overall, the process of drug safety signal detection, risk evaluation, and management, collectively referred to as pharmacovigilance, is an important part of the drug lifecycle, and health care providers, as well as patients and caregivers, play a critical role in this process.[2,9,16]

Dr. Birnholz:
Well that's a great thought to leave with our audience and I very much want to thank my guest, Dr. Jessica Ailani for helping us better understand pharmacovigilance.

Dr. Ailani, it was great speaking with you today, thanks so much.

Dr. Ailani:
Thank you, it was my pleasure being here.

Announcer:

This program was sponsored by Amgen. This is ReachMD. Be part of the knowledge.

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