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## Diving into Drug-Induced Liver Injury: What We Need to Know

Dr. Buch:

What was it like when one of your patients experienced a drug-induced liver injury? Were you worried? Drug-induced liver injury, or DILI for short, continues to be one of the leading causes of acute liver failure, which is why today we're speaking with one of the world's leading experts on this topic.

This is *GI Insights* on ReachMD. I'm Dr. Peter Buch, and joining me today is Dr. Naga Chalasani. Dr. Chalasani has published hundreds of articles, numerous guidelines, and is the David W. Crabb professor of Gastroenterology and Hepatology at Indiana University School of Medicine. Dr. Chalasani, it's great to have you join us here today.

Dr. Chalasani:

Oh, I'm happy to be here, Dr. Buch.

Dr. Buch:

So Dr. Chalasani, let's start at the beginning. Can you discuss the difference between intrinsic hepatic toxicity and idiosyncratic hepatotoxicity?

Dr. Chalasani:

Yeah, sure. Intrinsic hepatic toxicity implies a compound is intrinsically toxic to the liver. It is the matter of the dose one takes. For example, acetaminophen is a prototype for intrinsic hepatotoxicity. If a person takes more than recommended toxic doses, they will get liver injury; whereas idiosyncratic is a type of liver injury where it is a rare, unexpected, and unrelated to dose. It's the idiosyncratic DILI that continues to be a challenge to clinicians and the pharma, as well as the regulators.

Dr. Buch:

And what are the phenotypes of DILI?

Dr. Chalasani:

So DILI is one that can mimic any type of liver disease; therefore, DILI must be kept in the differential, when one sees a patient with either new-onset liver disease or somebody's liver disease gets worse. Two common phenotypes are, one, that somebody presents with increased liver enzymes, whether an increase in AST, ALT, or increase in alkaline phosphatase. The other is patients present with the jaundice. And these are the two common phenotypes, but there are other important phenotypes that your audience must keep in mind. It could be acute liver failure, as you said at the beginning that DILI is one of the most common causes for acute liver failure. And it can present as the autoimmune hepatitis. So anytime one is evaluating newly diagnosed autoimmune hepatitis, they should keep in mind that it could be due to a medication. For example, minocycline, and the third is it can present as chronic liver injury even as a cirrhosis.

So the bottom line is that DILI can mimic any type of liver disease; therefore it must be kept in the differential by every gastroenterologist when they're evaluating patients with liver disease.

Dr. Buch:

With those phenotypes in mind, Dr. Chalasani, how do you make a diagnosis of DILI?

Dr. Chalasani:

Fundamentally, high index of suspicion and it is a diagnosis of exclusion. So the clinical scenarios are it needs to match, meaning that there is a temporal association. Somebody has been placed on a new medication within the prior 12 to 16 weeks. And then one excludes competing etiologies of liver injury. For example, if somebody presents with a hepatocellular type of liver injury, or one must make sure

we are not dealing with viral hepatitis or autoimmune liver disease and so forth; whereas if one presents with cholestatic type of liver injury where alkaline phosphatase and bilirubin are high, one must keep in mind obstructive type of jaundice, meaning either there is a stone in the common bile duct or malignancy or even sort of an infiltrative process.

So to sum up, high clinical index of suspicion, and excluding sort of the common competing etiologies.

Dr. Buch:

For those just joining us this is *GI Insights* on ReachMD. I'm Dr. Peter Buch, and joining me today is Dr. Naga Chalasani, who's discussing drug-induced liver injury, also known as DILI.

Now Dr. Chalasani, can you tell us about the relationship of NASH and DILI?

Dr. Chalasani:

Our understanding in this area is continuing to evolve. And there are some epidemiological studies suggesting that NASH may predispose individuals to DILI. However, at this stage, the data are a bit soft, but I would like your audience to know a few things. Statins have been proven to be very safe in patients with NAFLD or NASH. Therefore, if a patient with NASH or NAFLD has dyslipidemia, they need statins, I think they are safe. However, for patients with NASH, it is good that they avoid certain medications, for example, methotrexate or tamoxifen.

So at this stage, I would say the relationship between NASH and DILI is compound by compound, and an excellent source, for clinicians, can be a liver-tox-dot-gov. It's a fantastic resource by the National Library of Medicine and is led by Dr. Hoofnagle from the NIDDK.

Dr. Buch:

And would you kindly review the concerns regarding dietary supplementation and the liver?

Dr. Chalasani:

Sure. Liver injury due to herbal and dietary supplements is increasing and the frequency over the course of last 20 years or so. I would like to share, with your audience two sets of data. One is our own research experience in the drug-induced liver injury network. Over the course of last 20 years, the proportion of liver injury due to herbal and dietary supplements has risen by anywhere from five- to to six-fold. The second piece of alarming data is also published by us showing acute liver failure needing liver transplant waitlisting has risen by eight-fold over the course of last 25 years. About 20 to 25 years ago, about 3% of acute liver failure needing to be placed on the transplant list was due to herbal and dietary supplements. More recently, a fully 25% are due to herbal and dietary supplements about an eight-fold increase. So that's certainly concerning.

I'd like your audience to know though the culprits are constantly evolving. For example, –Herbalife, OxyELITE Pro, and Hydroxycut were sort of the prototypes for herbal and dietary supplement-related liver injury. However, though, over the course of last three to four years, for example, green tea extract, not the green tea one drinks, but just the extract for as to promote weight loss has sort of become a very important cause for acute liver injury. And within the last year or two, curcumin, which is sort of an ancient spice, is turning out to be hepatotoxic just because the formulation of curcumin now has much higher bioavailability. The spice one takes is not absorbed, but the manufacturers are adding things like black pepper to make it more bioavailable. So that is causing hepatotoxicity.

So I think one sort of needs to keep sort of an open mind into the new culprits that are evolving in the field that in terms of dietary supplements that are leading to DILI and acute liver failure.

Dr. Buch:

Along the same line of thinking, what trends are you noticing with dietary supplementation and liver transplantation?

Dr. Chalasani:

What's been observed is that the label on the bottles is oftentimes inaccurate, either in terms of the ingredients or just the in terms of just a quantity. So for example, just a vitamin, if you take 100% of daily recommended dose, it's not expected to be toxic. But if you take the same thing or 10,000% of what's recommended, it can become toxic. So I think the adage that too much of anything is just not good.

Dr. Buch:

Now we're almost out of time, Dr. Chalasani, but before we close, are there any additional insights you'd like to share with our audience?

Dr. Chalasani:

Yeah, as I just said a moment ago, I think over the course of last quarter century, the acute liver failure due to dietary supplements requiring to be placed on a transplant list has risen by 8%. About 20 years ago, 3% of all cases of acute liver failure needing on the transplant list were due to dietary supplements. Now it is up to 25%. Two big groups of supplements cause DILI: one is weight loss

supplements. You know people are taking green tea extract, Herbalife OxyELITE Pro, and so forth. Here, the type of liver injury is hepatocellular. High liver enzymes such as AST, ALT, and jaundice, and coagulopathy. The other, group is body-building agents, like anabolic steroids. Here, people get profoundly jaundice. And typically, this takes time, but most patients recover after months and months of suffering with jaundice and the itching and maybe clay-colored stools.

Just one thing I would like your audience to keep in mind is the high index of suspicion. A careful drug history in addition to what the patients are taking that are prescription, probing them about over-the-counter medications, as well as herbal and dietary supplements, I think can be revealing.

Another thing I would just say though is when once is a newly diagnosed autoimmune hepatitis, seeking careful history can uncover sort of unsuspected drug-induced autoimmune hepatitis.

Dr. Buch:

I want to thank Dr. Naga Chalasani for sharing his expertise with us. Dr. Chalasani, it was great speaking with you today.

Dr. Chalasani:

Likewise, Dr. Buch. It's been a pleasure.

Dr. Buch:

For ReachMD, I'm Dr. Peter Buch. To access this episode and others from this series, visit [reachmd.com/giinsights](https://reachmd.com/giinsights), where you can Be Part of the Knowledge. Thanks for listening, and see you next time.