Patients with pre-existing liver disease *should* be included in clinical trials prior to drug approval

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DR. PEARS: Thank you. The next speaker is Dr. Will Lee, who is well known to all of you, from the University of Texas Southwestern Medical Center. He is going to talk to us perhaps more from the patients' perspective about what the risk may be to patients of including them in clinical trials.

DR. LEE: Thank you. It's always a little daunting to get up here without any data to support one's talk, and that's the situation that I'm in today. But John always gets us to give some talk with a funny title, at least to me, that has not as much data in it as I would like to have. So with that preamble, let me just try to approach this from the point of view of some cases studies of situations that I've encountered serving on data and safety monitoring boards (DSMBs).

And, this will give you a little bit of a perspective of whether we can improve the honesty, if you will, of what we do in the preapproval setting, and whether we can develop more robust post-marketing surveillance. These are true stories. A lot of the people who were involved in the DSMBs, like Jim Freston, are in the audience. So if Jim pops his hand up in the middle and says, no, it wasn't like that, he's probably right, but at any rate, we'll keep going.

The main issue: Are trials too homogeneous? Answer: yes.

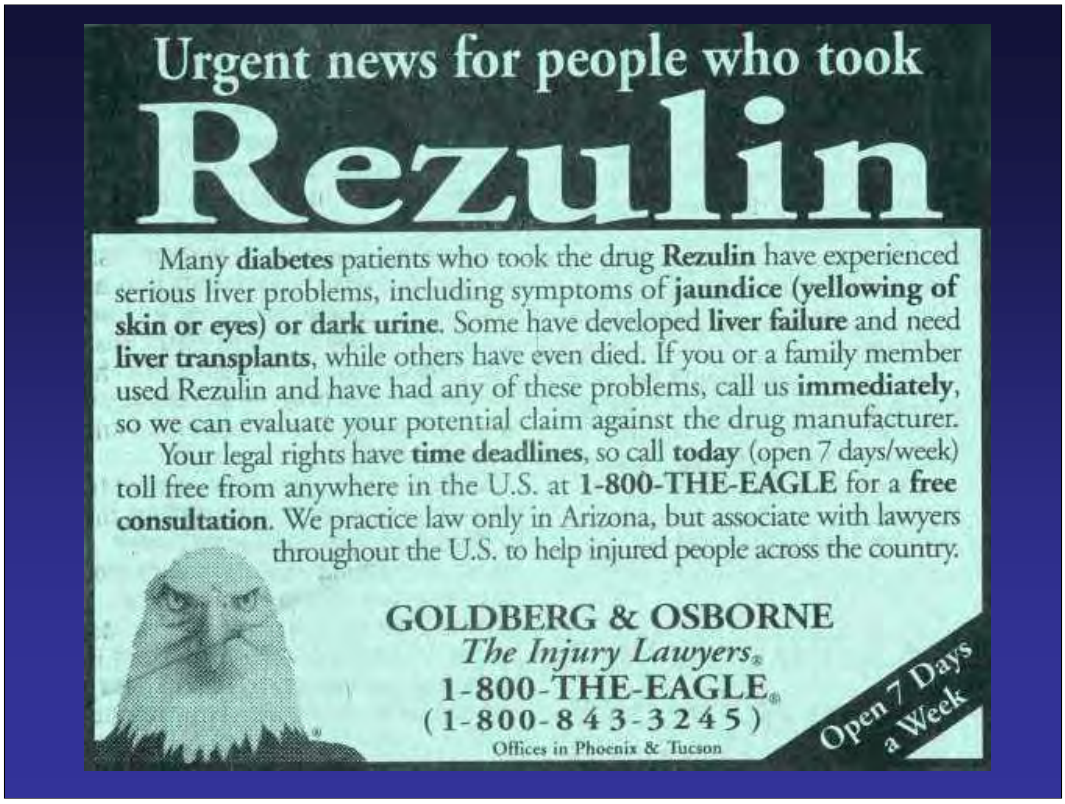
- **Patients with the disease in question must be included but:**
- **Nothing else, no hepatitis, no HIV, no elderly, no heart failure, no renal failure.**
- **This provides short-term relief and later pain!**

The main question that I posed or that I felt was posed was: “are the clinical trials that we perform too homogeneous?” My take on it is that the answer is yes.

Three case studies:

- **Troglitazone: unanticipated heart failure. What to do?**
- **Duloxetine: unanticipated association with alcohol. Is there a synergy here?**
- **Ximelagatran: co-morbidity occurring in a trial, but unrecognized by monitors.**

Patients with the disease in question must be included. Obviously you can't test a thiazolidinedione without having a diabetic, but then you need to take into account all the other comorbidities that are seen in the diabetic population. Typically in the preapproval setting, we try not to get anyone without any comorbidities, knowing full well that once approval takes place, all of these people are in play. So my point is that you may have short term relief in this clean, preapproval trial that gets your drug to approval and then you pay the price later on by having all the complications show up after the drug has been marketed. Again, this may be, in fact, an argument for easier drug approval and more post-marketing surveillance, or for a more robust post-marketing surveillance system. So here are the three case studies that I've been involved in: the first drug was pioglitazone, and the second was duloxetine. These were both post-marketing situations where unanticipated problems came up that required new sort of paradigms to deal with them. And the ximelagatran situation, which was touched on yesterday in the eDISH discussion, actually had some interesting cases come through during the preapproval process that really represented other clinical liver diseases, but because they were embedded in the set that was seen as having hepatotoxicity, they were I feel misdiagnosed in that setting. We can talk about that a little bit.



So let's talk about the thiazolidinediones. You all recall Rezulin was the first in the class and led 1-800-THE-EAGLE to go on a hunt once Rezulin had been on the market for a while for these very severe cases of liver toxicity. Indeed there were cases, and it's of interest that in this setting most of the cases that we found in the ALF study group, as was mentioned yesterday, were found during the first year. I take the point made that I don't know that monitoring helps, but awareness of physicians that there's a problem with the drug, of course, may sink the drug, but it may also heighten earlier identification of cases. That's all hypothetical.

Case study 1: Troglitazone: liver disease vs. heart disease

- Pre-approval: some Hy's law cases
- Post-approval: definite acute liver failure
- Troglitazone remained on the market while other drugs were in development.
- Question of heart failure and CV collapse:
- Were these cases related to TZD's?

But at any rate, it was clear that troglitazone had a liver signal. There were some Hy's Law cases and, of course, post-approval there were definite acute liver failure cases. However, if you recall troglitazone was approved in 1997 and pio- and rosi-glitazone were both in development but had not been approved. Rezulin was the first in a new class of drugs. It was highly regarded as a new therapeutic entity, and there was a lot of enthusiasm among the diabetologists. Our senior diabetologist at the University of Texas Southwestern, Phil Raskin, is still annoyed that troglitazone was pulled off the market. So the question really came up later on, were pio- and rosi-, would they have the same signature as troglitazone did? You know now they didn't. It was kind of interesting that the first drug in the class had this hepatotoxicity issue but the next two seemed not to have.

Thiazolidinedione heart disease

- Several cases of pulmonary edema and ARDS occurred, usually in elderly with co-morbidities
- Was there any relationship to: liver (no), increasing heart failure (maybe)
- But use in the elderly is going to occasionally be associated with terminal episodes.
- Fluid retention might have been a factor.

However, they all seemed to have a question of heart failure and cardiovascular collapse. Jim and I were part of the DSMB that was reviewing cases of pioglitazone through this sort of late preapproval and then in the post-approval period, where we would repeatedly get cases that were advertised as possibly having liver failure when they were 88 year olds coming in with a myocardial infarct and sudden death. Now that could have some relationship to the thiazolidinedione. It certainly wasn't liver failure but again it raised a post-marketing issue of whether there was a kind of cardiotoxicity, if you will, related to these drugs.

So there were several cases that we were looking at with pulmonary edema and ARDS. They were usually very elderly and again I would submit that these very elderly patients post-marketing, never would have been included in the preapproval process. But was there any relationship to liver disease? We agonized over the first few, but then we sort of saw a pattern. They really were coming in with heart failure or cardiovascular collapse, and didn't have any kind of hepatic injury other than what you would see if they were to survive more than the first few hours past the emergency room.

So use in the elderly is going to be occasionally associated with terminal episodes, because elderly people are like that. But fluid retention might have been a factor here, and it was really hard for us as hepatologists to appropriately address this. However, the fix for this was to appoint a separate data and safety monitoring board made up of cardiologists. I think they adjudicated these cases and thought that there might be some association. Again, this is in part reflecting the elderly population that were put on the drug post-approval but hadn't been identified preapproval.

Why not know about this during clinical trial?

- **Controlled environment.**
- **Very careful monitoring.**
- **Not an uncommon side effect.**
- **All the permutations of this could have been anticipated.**
- **Why were these issues not raised?**

So again, the preapproval clinical trial, is a very controlled environment. There is careful monitoring, and maybe this isn't really the setting to put the over 80 patient in if you imagine that this patient is going to receive your drug after approval.

You know, you're not going to see uncommon side effects unless you have a wide range of patients. All the permutations could have been anticipated. You know, if you look at your patient population, what diabetics look like. They tend to be older. They tend to have coronary artery disease. They tend to have renal insufficiency. So if we set up the trial to exclude these kinds of individuals, then we're setting it up for success to get the drug approved, and problems will be found post-approval.

Etiquette of the clinical trial

- **Bring up nothing controversial.**
- **Don’t go looking for side effects.**
- **Monitor closely, use a worthy comparator (preferably one with its own problems).**
- **Keep it simple.**
- **Don’t use in any controversial population.**

So perhaps this is going to be controversial in itself, but I would say that the etiquette of clinical trials, and the way we're designing them now, is to keep them as clean as possible, don't bring up anything controversial, do your AST or ALT monitoring but don't look for funny side effects. Keep it simple and again certainly don't use a controversial population.

Controversial populations

- Renal failure
- Elderly
- HIV positive
- Any chronic hepatitis
- Diabetes mellitus
- Congestive heart failure
- Alcoholics
- Pregnancy

Well, what are the controversial populations? Renal failure, particularly the elderly, HIV positive, any chronic hepatitis, diabetes, congestive heart failure. But all these people are going to receive the drug once the drug's approved. Alcoholics and I'll talk a little bit about this later on. Pregnancy and immunosuppression.

Case study 2: duloxetine

- SSNRI: Central antidepressant and pain inhibitory functions
- Metabolized by CYP 2D6 and 1A2.
- Metabolism slowed by presence of cirrhosis.
- Used as second tier drug for depression:
- Anticipate its use in combination with:
  - Other antidepressants
  - Alcohol
  - Cocaine/heroin/other narcotics/lithium
  - Many depressed people will have hepatitis C or fatty liver

So case study number 2, duloxetine. I was not involved in any of the approval processes for duloxetine, but I was involved in the post-approval period, again because the issue of hepatotoxicity, which should not have really been raised pre-approval, came to the floor in the post-approval setting. So as many of you know, this is SSNRI, selective norepinephrine re-uptake inhibitor, works as an antidepressant and has an indication for neuropathic pain, diabetic neuropathy and so forth. It is metabolized by CYP 2D6. We know that the metabolism is slowed in the presence of cirrhosis. It is used as an antidepressant, perhaps not in the first tier, but coming to be more commonly used. I'm told that over 12 million prescriptions have now been written for duloxetine.

So what would you say, if you're going to use it in depressed people, what does a depressed population look like? Well, they're going to be on other antidepressants, there's going to be a lot of alcohol use, and there's going to be a lot of substance abuse as well as use of narcotics, lithium and so forth, and there will be lots of people with hepatitis C or fatty liver disease. You hepatologists know that the hepatitis C patient population is fraught with lots of depression, lots of other issues that we deal with every single day, but let's look at the depressed population. Many of them are drinking; many, many of them are not telling their doctors how much they drink.

Post approval of duloxetine

- **Cases suggesting liver effect but:**
- **No case was unconfounded by severe alcohol use**
- **Or acetaminophen plus alcohol.**
- **No ‘clean’ cases were seen.**
- **Lesson: Consider the patient population(s) that will be receiving the drug, not just the condition that will be treated.**

So post-approval, because there was this apparent liver effect, the data and safety monitoring board was formed. We could not find over the course of two or three years any clean case, that is a case of hepatotoxicity that was not confounded by alcohol, and I think it just reflects the patient population. If you're going to get it into 6 million people, there’re going to be a few cases of severe alcoholic hepatitis, even some fatal cases, and this is what we saw. The ones that were not severe alcoholic hepatitis, had acetaminophen on board. They had the aminotransferases in the 5,000 range, and were clearly in all likelihood taking acetaminophen overdoses or this unintentional overdose that we've talked about so much.

Delay by HealthCanada: duloxetine

- **Concern continued to be raised after approval in US and EU.**
- **All post-marketing reports from the US were reviewed.**
- **Once again, no ‘clean’ cases were seen.**
- **Lesson: This was viewed by HealthCanada as continuing associated damaging data.**
- **The DSMB considered it ‘noise’.**

We didn't see any clean cases and again I would posit that somehow we need to get into preapproval processes these complex patients that are going to appear post-approval. So what happened was, and this isn't a huge crime, but Health Canada got very excited about this. Duloxetine had not been approved in Canada even two or so years after it had been approved by the EU and US, there were a lot of post-marketing reports coming in, but again of 40 or 50 reports, they all seemed to have the flavor of, of either a pure overdose like acetaminophen, fatal, suicidal attempt, or they had heavy alcohol, binge drinking for the month prior to being evaluated. I think the FDA understood this, although initially Health Canada did not understand it but finally they were convinced. I'm not sure why they finally reversed themselves, because the last I had heard, they had turned us down. But duloxetine is now approved in Canada and Australia.

So again the duloxetine story was I thought fraught with questions because in the preapproval process, there probably were not enough random depressed people rather than sort of pure uncomplicated depressed people. Now that's very subjective, of course.

Case study 3: ximelagatran

- New class of drug, a thrombin inhibitor
- Requires no monitoring, one dose fits all
- The coumadin population is fraught with major hazards:
  - Heart disease, atrial fibrillation, DVT
  - Elderly
  - Difficult to manage co-morbidities

So what about ximelagatran? This was a thrombin inhibitor, representingd a new class once again. By the way, I think it's obvious by now, the first in class is the one that's the canary in the mine. It's the one that shows you what the pattern is going to be for hepatotoxicity going forward. It may or may not be the worst in class, but as troglitazone proved, it had more hepatotoxicity than later drugs in the class.

But in any event, I served on the data and safety monitoring board that was formed preapproval when there clearly was a signal in the Phase II testing. We adjudicated a lot of cases very carefully during the large database, over 12,000 patients, 6,000 on drug, about 6,000 on Coumadin, that took part in these trials.

Now what did that population look like? It was a very tough population, and this is in part the reason that this drug never made it. It's because this was a real world population and included 80 year olds. If you needed the drug for atrial fibrillation or DVT, you were already a compromised heart patient, and you tended to be elderly and you probably had lots of comorbidities, but let's put it in perspective.

Ximelagatran was intended to be a one-size-fits-all drug. There were issues about the dose,; I can't address those and it's not appropriate today, but the point is, it would be hugely successful as a replacement for Coumadin. Coumadin is one of the worst drugs we use. It's estimated that up to 50 percent of people who could benefit from Coumadin never receive it because they can't manage it. That's certainly true in our Parkland population.

The second feature, as I guess you all know, it takes about a week to get someone up to speed on Coumadin, and that typically is a week spent in the hospital. So there are a number of difficulties with Coumadin that I think were taken into account but perhaps not enough in my view.

Case study 3: ximelagatran II

- 7.9 % had aminotransferases ≥ 3x vs. 1.2% for comparator (>6,000 in each group)
- Hy's Law cases = 37, of whom 10 died, 9 of unrelated causes, one with bleeding, one with hepatitis B: age of these patients were 80 and 77, respectively.

Now as you heard yesterday, aminotransferases were elevated three times in nearly eight percent of cases and this was certainly higher than the comparator. There were a bunch of deaths, but 9 of them were from unrelated causes. There was the one liver case that you heard about yesterday, an 80-year old who died of a bleeding duodenal ulcer, on corticosteroids but he also had been lost to follow up. He left the physicians that were caring for him and died in another hospital.

And the case I wanted to point out, which perhaps was an outlier, but it certainly colored the whole view, in my opinion, of what happened at the Advisory Committee meeting. I wasn't there, by the way. It was a case of fulminant hepatitis B, a very clear-cut hepatitis B case. It was a person with lupus who was on two kinds of immunosuppression and had an acute flare and died of fulminant hepatitis B, a classic situation that we all recognize. This was still classed as a DILI case, and there's no way that I think most hepatologists would consider that this had anything to do with ximelagatran.

Message from case study 3

- While aminotransferase elevations were common, most were self-limited
- All deaths were compromised cases: Hep B case should not be included. Even the case of severe liver injury was compromised by being elderly, non-compliant, dying from other though possibly related cause.

So there certainly were transaminase elevations. You know that most of these seem to be self-limited and went back down. My concern was that the hepatitis B case occurring in the preapproval trial still colored to some extent what was happening later on. And again, by the way, this patient was something like 78 years old.

Message from case study 3, cont'd.

- Drug trials are a crap shoot
- We go into them as if they are being performed on healthy people
- At the same time, we hand select cases to avoid problems
- More consideration should be given to what the drug's proposed population looks like and whether they will profit from the drug, in spite of side effects.

So drug trials are a crapshoot. It's a hard business to be in. I take my hat off to the pharmaceutical companies who persist in trying to put forward good drugs in this environment, which is very hard. We think drugs are being tested on healthy people. As I've shown you, some of the patients in the ximelagatran trial clearly should never have been enrolled, if you take the pure point of view that only ideal patients should be involved so that we get a clear picture of what the true signals of the drug are. At the same time, if we hand-select the cases too much, we're avoiding the problems later on.

Conclusions I

- **Enroll all patients that fit the diagnosis of the condition, regardless of their co-morbidities.**
- **Make it clear that you are including them for 'real world' data.**
- **Do not exclude patients that have any underlying liver disease if they fit the patient profile expected to use the drug.**

I think we need to consider what the real-world population is that's going to be taking this drug. I will posit that the company in this instance, because they had to use it in patients with atrial fibrillation, had to pick typical cases that were severe, that were elderly. In this setting, they set themselves up for failure in a way, because they couldn't restrain and keep in line the patient population to keep it clean. But having said so, I think it's our responsibility in adjudicating these cases to make the right calls and say this was not a ximelagatran case or this was but here's an other extenuating circumstances, not to take them completely off the hook.

So ximelagatran might have had its place if we had known how to handle it better, to recognize that there was high risk but also high benefit. I think people alluded to that sort of approach at the end of the day yesterday. Coumadin is not a great drug. It's one of the worst drugs we have. It would be lovely to get rid of Coumadin, and since Coumadin basically requires all these prothrombin time measurements, certainly in the first few weeks of therapy. Weekly aminotransferase monitoring probably could have been performed in similar fashion to what is occurring with Coumadin.

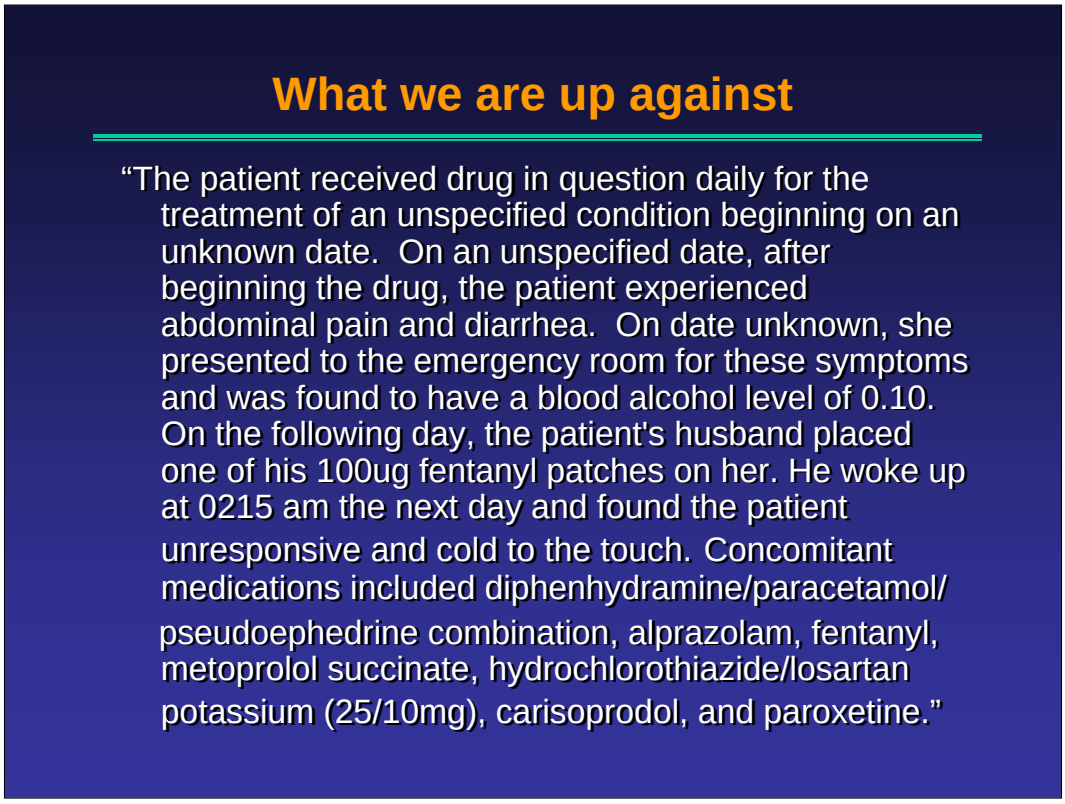
Conclusions II

- **FDA and Pharma should agree up front on the ground rules for enrolling at risk patients in the suspect group.**
- **This would allow a more realistic experience that mimics post-marketing**
- **Advisory committees should consider these factors as important and cut the companies some slack for these imperfect studies.**
- **This is real world after all!**

And I would argue that perhaps what we need to do is to be a little bit more liberal in approval but tighter in giving us something like a provisional approval that then leads to final approval later on when a larger subset of patients has been enrolled.

So again, I touched on this a second ago. Could there have been a provisional approval? Say, okay, this is a great drug, we see this aminotransferase signal. We also have seen a couple of muddled hepatotoxicity-with-death cases, but most of the deaths were related to heart disease and other things. We'll give you provisional approval if you put in place a very stringent risk management system, and again the example yesterday was agranulocytosis. The kind of monitoring that we've never done in the liver setting but we may need to think about. So it would have to be close monitoring mandated in a larger population and we just don't have those kinds of systems in place right now. But post-marketing surveillance would have to be beefed up if you're going to take this kind of process seriously.

Now again to look at the patient populations at risk. If you have a cardiovascular drug, and ximelagatran was a cardiovascular drug, the patient population is going to be elderly. There is risk of sudden death, and I would posit that also the advisory committee had mostl cardiologists and pulmonologists on it, and there weren't a lot of hepatologists in the room that day, but that's an aside.



Diabetes mellitus again occurs in an elderly population. They're obese. Many have coronary artery or biliary tract disease. The depressed population, I touched on. So if you look at an antibiotic population, it probably is better. It's not going to be necessarily elderly but it's going to include a few elderly. The NSAID population is going to be athletes and people with osteoarthritis. The hypertension population is going to have diabetes, cardiovascular disease, and be elderly again. I'm just sort of setting the tone, that if you're looking at an antihypertensives, it's going to be a relatively fraught with risk population. Certainly, the HIV population is riddled with hepatitis signals, and we still have trouble interpreting them and so forth and so on. Certainly many of the anti-cancer drugs have big-time liver signals, but they're usually liver metastases and biliary obstruction.

In conclusion, I'm thinking that pharmaceutical companies ought to consider a wide range of diagnoses in preapproval to be less strict in terms of age and in terms of presence of liver disease and other comorbidities, but they have to make it clear and agree with FDA that they are going to include these real-world cases.

Do not exclude cases with underlying liver disease if they fit the patient profile for people that are actually going to be using the drug later on. Recognize the risk early, use a very good data-capturing strategy. We have that now. Employ a superb DSMB. That's obviously important to adjudicate the cases, and probably figure out what's going on, what is the signal, use standard causality assessment tools. The FDA has to learn to accept these more complex data sets.

Comparison of Different ALF Etiology Groups

N = 1,033

	ACM n 475	Drug n 119	Indeterminate n 151	HepA/HepB n=31/75	All Others n 182
Age (median)	36	43	37	47/41	41.5
Sex (% F)	74	67	56	45/44	76
Jaundice (Days) (median)	0	10	10	3/7	7
Coma ≥3 (%)	51	38	48	55/52	42
ALT (median)	4149	571	851	2404/1601	677
Bili (median)	4.5	21.6	23.0	11.9/20.8	15.2
Tx (%)	9	40	42	29/47	35
Spontaneous Survival (%)	64	26	27	58/24	30
Overall Survival (%)	71	63	65	84/64	60

Remembering, and this is the only data slide I have, that in the ALF study, the DILI cases all have median onset from jaundice to coma of 10 days. So there is time I would say, if you're proactive, to identify the cases, get them off the medication if necessary and so forth. The acetaminophen cases you never can. It's much too quick.

Two other quotes

- THE PATIENT HAD THE FOLLOWING LAB VALUES: ALANINE AMINOTRANSFERASE (ALT) = 1005, ASPARTATE AMINOTRANSFERASE (AST) = 848, BILIRUBIN = 2.5, CREATINE KINASE-MB = 35.6, CREATINE KINASE = 835, AMMONIA = 38, B-TYPE NATRIURETIC PEPTIDE = 3900, CREATININE = 3.7 AND BLOOD UREA NITROGEN (BUN) = 97. PATIENT WAS FOUND TO BE IN HEPATIC FAILURE.

- He is reported to have been obese with possible metabolic syndrome. Approximately 1 month later he was reported to start binge drinking and he is also reported to take acetaminophen, but there is no information about how much.

So I threw this in as just a sort of final coda. Here are some of the case reports that we looked over, and I'll just read it over very quickly. The patient received drug in question daily for the treatment of an unspecified condition beginning on an unknown date. On an unspecified date, after beginning the drug, the patient had abdominal pain and diarrhea. On date unknown, she presented to the emergency room for these symptoms and was found to have a blood alcohol level of 0.10. On the following day, the patient's husband placed one of his Fentanyl patches on her. He work up at 0215 in the morning and found the patient unresponsive and cold to touch. Concomitant medications, and there's a whole list.

I mean nothing's simple. Nothing's simple in this world.

Here's a couple of other ones. How do you adjudicate this kind of case? The patient had the following lab values, ALT 1000, AST 848, bilirubin 2.5, creatine kinase-MB fraction 35, creatine kinase 835, and so forth, BNP 3900. I haven't even heard of a 3900 BNP. Creatinine 3.7. Patient was thought to be in hepatic failure. No, this was heart failure. This was renal failure. Maybe a touch of liver failure. Anyhow.

Finally, this is the last one. He is reported to have been obese with possible metabolic syndrome. Approximately 1 month later, he was reported to start binge drinking. He also reported to take acetaminophen, but there's no information on how much.

Conclusions for FDA reviews

- **Consider the complexity of the trials and real world medicine**
- **Specifically, consider the patient population that will likely be utilizing the product**
- **Get the best advice from clinicians concerning all the nuances of these situations**
- **Keep a real world context in mind at all times!**

So again, these cases just emphasize that we must have more detail. We have to have very active reporting and if we do so, we'll see how complicated the cases are, but we'll also have a better handle on them.

I think this is my last slide. We should agree up front that these patients aren't simple to study. There probably won't be enough alcoholics in a depression study for a subgroup analysis. It's impossible, but it was something that Health Canada wanted us to do, to set up a study of Cymbalta in alcoholics. You just can't do that unless you fold them into a larger clinical trial, I would argue.

But I think advisory committees need to be more open to the complexity of what's going on these days and that even the preapproval trials are still real world medicine.

Study Sites (Adult) in the ALFSG 2006

UT Southwestern	Lee/Polson/Pezzia
U Washington	Larson/Do
UCSF	Davern/Moawad
Mt. Sinai NYC	Martin/Karabicak
Univ Nebraska Omaha	McCashland/Bernard
Baylor Dallas	Murray/Lepe/Coultrup
Univ Pittsburgh	Shakil/Morton
Northwestern Univ	Blei/Gottstein
OHSU, Portland	Zaman/Ingram/Aby
UCLA	Han/Kim/Peacock
Michigan	Fontana/Welch
Univ Alabama Birmingham	McGuire/Avant
Mass General	Chung/Rutherford/Bihrle/Sui
Columbia/Cornell NYC	Schilsky/Saravia/Gomez-Pichado
VCU	Stravitz/McLeod
Mayo Clinic: Rochester, Jax	Hay, Raj: Groettum/Kontras
UC Davis	Rossaro/Prosser
Einstein Philadelphia	Munoz/Riera/McGill
MUSC Charleston	Reuben/Huntley
Pennsylvania	Reddy/Campbell/Elliott
UCSD	Hassanein/Barakat/Petcharaporn
Duke	Smith

Let me just stop there. Thank you.

(Applause.)