

## OFF-LABEL DRUG USE: PROS AND CONS

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Thank you. I'd like to thank Rebecca Solomon and the *Journal* for their invitation today to join such a distinguished group of individuals. It's funny because I tell my students every day in practice you ought to be able to learn something, so I'm here to learn as much as I am to contribute. But thank you very much Rebecca for the opportunity today.

What I'm going to do is talk about how the FDA got its start, what labeling means, what off-label means, give you some examples of some of those off-labeled uses, and then give, from my perspective, some of the pros and cons of off-label drug use. I admit I do not have all the answers by any means, but at least hopefully I'll have some food for thought. And then if we have the time I'll talk about some specific off-label uses of drugs that we use in our endocrinology practice without really thinking too much about it because it just makes so much sense to do.

But to give you a little background, in the summer of 1906, the Pure Food and Drug Act was passed by Congress. If anyone remembers back to Upton Sinclair and Samuel Adams—not that Samuel Adams, but another Samuel Adams—there were several exposés looking at the problems in America with the meat package industry and abuses of workers. This, along with some drug issues, actually initiated this legislation which was food for the beginning of the Food and Drug Administration, or at least what eventually became the Food and Drug Administration. Actually many people will pick the date this legislation was enacted, as passed by Congress, as the true start of the FDA, although it actually wasn't named that until several years later. But basically this legislation gave responsibility to the FDA to make sure that food and medications were labeled correctly.

In 1906 it was okay to sell cocaine. It was not a problem as long as it was appropriately labeled. Coca-cola got into a problem because even though they had minute amounts of cocaine in their Coca-cola, it was the fact that they didn't disclose there was a lot

of caffeine. That was a problem. So it's amazing how things have come around, but again just some of the history. I was going to be a history teacher when I was growing up and it didn't work out that way, so sorry if I'm boring you with the extra details.

The Pure Food and Drug Act was supplanted by the Federal Food Drug and Cosmetic Act in 1938, in which Congress gave the FDA the authority to regulate the safety of food, drugs and cosmetics. Unfortunately, this came as response to what was going on in the day: in 1937 there was an elixir of Sulfanilamide, an antibiotic that was concocted by S.E. Massengill Company. But diethylene glycol was used as a solvent to make this elixir. Now, the FDA went after the company for fraudulent labeling because elixir implies alcohol and there was no alcohol in Elixer of Sulfanilamide, so they got them for labeling problems. But the real issue was that over a hundred people died, most were kids, because of diethylene glycol poisoning. Up to that time, a product did not have to demonstrate safety to make it to the market. Because of this tragedy and the subsequent outcry, the FDA and Cosmetic Act were passed in 1938. So again, it's often time responses to events.

Finally, the DESI Amendment passed in 1968 and, actually filed as the Kefauver-Harris Amendment of 1962, was passed after another tragedy. Dr. Scarpace alluded to it when she talked about the Thalidomide tragedy. You had thousands of kids born with birth defects as a result of their moms having taken Thalidomide for nausea during their pregnancy. Because of that issue, in addition to safety concerns, current legislation requires companies to prove their efficacy of drug therapy before it makes it to market. So from a labeling issue, evolved into safety concerns, and finally to proving safety and efficacy, we've seen the evolution of the FDA as time has gone on.

What the FDA approves in the package insert for each medication is the quote, "approved indication." The drug label contains information about the drug, including the approved dosage and how it's to be given to treat the particular medical condition for which it was approved. When we talk about off-label use, we talk about something that isn't compliant with those specific recommendations. When a drug is used off-label, it is most commonly given for a different disease or medical condition than described in the FDA-approved label. I'm going to give you a number of examples of that in just a couple more

slides, okay?

It's important to realize that, as Dr. Scarpace mentioned earlier, the off-label use of drugs is not regulated by the FDA. In fact, the FDA has nothing to do with this. It is up to the clinical judgment of medical practitioners if they want to use something off-label. I'm not going to get into the liability issues, because that's going to be another discussion for panel number two today, but the point I want to make is just because something is off-label doesn't mean it's incorrect.

Now, depending on that decision and how much data is there to support it—what about the safety concerns? Even more interesting is the number of treatment guidelines. So you look at the consensus guidelines for the number of disease states—and I'll give you an example of this a little bit later on as well—is the guidelines actually sometimes recommend for the use of particular drugs in certain situations when they have no FDA approved labeling for that. So, i.e., they are being used off-label.

Off-label is certainly not necessarily a bad thing, but it really depends, and we'll talk about some of the specific examples. So, for instance, Quetiapine or Seroquel is an antipsychotic, all right? It was originally approved for schizophrenia, while it is often used off-label for the treatment of depression. Is it effective? What about the safety issues? Typically, it's been used in the treatment of depression for Alzheimer's patients. Well, now there's a black box warning indicating that elderly patients have a higher risk of sudden death with the use of these types of drugs. That's a bad thing. So again sometimes when these drugs are used off-label there just isn't the safety data there to demonstrate that there's not going to be a problem.

All right. So often when we think about using drugs off-label we think about specific indications for a different disease state, but that isn't always necessarily is the case. The next example is with Paroxetine or Paxil. This is a medication used for depression. However it's not labeled for use in pediatrics, all right? When it's used in pediatrics, that's an off-labeled use. So this is an off-label use of an approved medication for the treatment of depression. It just happens that there are no studies in patients of that age, so it's off-label use.

Sometimes there is an extrapolation that if a certain class of medication is used for a particular indication, the next new drug in that class which becomes available is probably beneficial in that respect as well. For instance, angiotensin-converting-

enzyme inhibitors, it's just a kind of an extrapolation that the next ACEI that is only approved to treat hypertension, would be effective for the treatment of diabetic nephropathy as well. Another example is the ACEI monoxapril. Monoxapril is not approved for heart failure, but is approved for hypertension. Sometimes patients or clinicians will use this off-label for heart failure because we have at least five other ACE inhibitors that are actually approved for both hypertension and heart failure. So again, a little bit of an extrapolation. Although if you're going to be purely evidence-based and you say, "Well, you know, the proof is in the pudding, show me the data," there is none in that case.

Sometimes a drug may be used for an indication. For instance, an antibiotic is indicated for the treatment of pneumonia. Well, bronchitis is an even less severe lung infection so presumably it's going to be as effective for bronchitis as well. And while theoretically it kind of makes sense, it would be, again, off-label drug use. Along those same lines we have extension to related conditions, Montelukast, or Singulair, is approved for the treatment of asthma. So when you think about the reactive airway component of COPD, a lot of practitioners have used this also in the treatment of COPD. Again by extrapolation. There are no data to demonstrate its efficacy. There's certainly not an indication for its use in this indication.

Gabapentin or Neurontin is a medication that was first approved in 1993 for the treatment of seizures, actually as adjunctive therapy for seizures, which subsequently got the indication for the management of herpes zoster post-herpetic neuralgia. It's also often times used off-label to treat Diabetic Peripheral Neuropathy. Again the extrapolation is that if it is effective for the treatment of one type of neuropathy, why not use it for something else? So another example of off-label use.

Sometimes we think physiologically of how things work. Pre-diabetes, a patient with type 2 diabetes has a disease of insulin resistance. We have medications that can lower insulin resistance. And so the fact that Metformin and Actos are two medications that are actually approved for use in the management of type 2 diabetes, we actually will use these in patients who are predisposed to diabetes. These are patients with blood sugars that aren't high enough to be considered to be diabetic, but not low enough to be normal. Our pre-diabetic patient will utilize these medications in an attempt to prevent

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diabetes. Now, lifestyle changes, such as exercise and weight loss, are even better, but again, sometimes that's not going to be doable for a particular patient. Again, another off-label use of meds.

And finally as an example: aspirin for the prophylaxis of cardio-vascular disease in patients with diabetes is an off-label use. I tell my students, typically if a patient has type 2 diabetes and is over the age of forty, even over the age of thirty, you need to say if they're not on Aspirin—why is that? Is there a contraindication? There is no labeled indication, but data suggest there's a clinical benefit there. So we use a lot of things off-label. In fact the prevalence of off-label drug use is enormous. In some estimates, depending on the patient population, up to 60% of drug use is estimated to be off-label. Often we think about it as the off-indication, but that takes very different forms, so it may be a different dose or the fact that something's used in a different age group, pediatrics for instance. A lot of different examples where it may be used something off-label besides just the indication.

Off-label drug use has been known for a long time. A 1985 study showed that of the one hundred most common uses of marketed drugs, 31% were for off-label use. A newspaper investigation in the late '90's and early 2000's demonstrated consistently about one out of five medications are used off-label, and this is just basically for the indication, not for the dose or for the group of which it was used in. Anticonvulsants, antipsychotics, and antibiotics were a large portion of that off-label use and we'll see a graph here in just minute demonstrating that. A study in 2006 demonstrated that of the 160 most commonly used prescriptions, again, one out of five was for off-label use. Interestingly and concerning to me is that 73% of indications were used without or very little scientific support. I don't have a problem using something off-label where there's some data to demonstrate its utility or potential safety compared to another therapy. But to just go off and say "let's just try it" – that's not good practice.

Then there's certainly specific patient populations that are very high risk for off-label use. You heard this already, high off-label use in the oncology population, the pediatrics population, the HIV population, the geriatric population, and the pregnant population. So there are a number of different populations where there are very little data looking at the utility of medications and

therefore don't have these labeled uses. However, a patient who's pregnant and needs to be treated, we need to use something. Often times we're a little bit handcuffed because we don't have these specific indications.

This is a study looking at off-label use in kids and I discern a little bit of a difference here. They talk about off-labeled use and off-labeled and unlicensed use. Basically the difference here is in the pediatric population, especially young kids and neonates, they can't do very well with swallowing tablets, so sometimes there is a concoction made, a different formulation of the drug made. You'd like to have stability data, you have to make sure the drug is being absorbed and there aren't any untoward events because of whatever you're using to make it into a different formulation, often that data just isn't available.

Now the proof is in the pudding. Is the patient responding to therapy? Are they getting better? Does there seem to be untoward events? And that's important to keep track of, it's important to realize that in some specific patient populations like pediatrics, especially neonates, up to 80% of medication use is off-label. Looking at this 2006 data, the most commonly prescribed medications used off-label include psychiatric meds, anti-asthma meds and allergy therapies. In some instances, 40% of use for a specific indication is actually off-label use of medications.

Now, if it's effective, if it has minimal side effects, if it's relatively cost effective, then off-label drug use is not a problem. It's when those three criteria aren't met that we start having more issues. From my perspective, some of the realities of off-label drug use include that once a drug goes generic, further studies will no longer be conducted. A drug company working with a compound, once it has the entity, has a seventeen-year patent life. Once that drug goes off patent, that's the end of it. There're some exceptions. If you get a pediatric indication, then the company has another six months of patent exclusivity. But for the most part you have seventeen years so all these medications are no longer patent-protected, they are off-patent that are generics with no incentive for manufacturers to conduct further research.

We talked already about specific patient populations with very high instances of off-labeled use just because of the issues. With oncology, and historically with the HIV populations, you're talking about people that sometimes are at the end of their ropes. There aren't many choices and we're willing to accept more side

effects. Think about oncology specifically, where you're talking about some of the most expensive and some of the most toxic drugs. Yet, in almost 75% of instances, this represents off-label drug use. Some patients are willing to take those risks for undocumented efficacy and potential for side effects because, well, what's the alternative? The alternative is I'm going to die of my underlying disease. So there're certainly disease populations where there are issues. Even veterinary medicine, where you have different species, outcomes with one species actually correlate with others. Again, a big question there.

So when I think about off-label drug use in our own practices at the Endocrine Group, there are two primary issues. One is if patient safety is compromised by off-label prescribing of medications. What we do is we look at the data, we look at the compendium, and we look at our own experience and we try to identify benefit and what is the relative risk. With all these decisions, I think that's the bottom line: is the potential benefit of our intervention likely to be successful and have less than the potential risk for it? And that's something I think we need to keep in mind. On the other hand, is patient care compromised by denying off-label use of meds? These two issues are where, in my mind, where the rub is. So if there are data available to address the particular scenario then that's great, but often for a specific situation we just don't have the data. And so we're extrapolating, we're taking maybe a little bit of a leap of faith. But the bottom line should be that at least our potential benefit outweighs the potential risk?

When you look at the issues with off-label use, it's a bunch of parties involved. One is clinicians who are looking to push the envelope. I can't wait for something for another three or four years for this new indication to be approved because I see the utility of this medication right now, I want to utilize it. Industry certainly, they're there to make money, we've heard that already. You know industry is there to make money. Now, they want to increase the market and sometimes they are a little too over the top with this. Pfizer got fined over \$400 million because of the off-label marketing of Neurontin. Purdue Frederick got nabbed for over \$600 million dollar for OxyContin. So there are some problems, but the point is industry is there to make money; they're there to make a profit, so we have to keep that in mind.

Payers increasingly want to identify the benefit of these therapies which are typically more expensive than what the

traditional or what has been considered to be the goal therapy in the past. And I think that's certainly appropriate. Patients want safe, effective medications. They also often want what's newest. So again, it's always a balance of what is the potential efficacy of these off-label treatments versus the relative risk. Sometimes we have some good information to kind of go with and sometimes we may not have as much information as we'd like.

So the pros and the cons. I think one advantage of off-label use is that it can kind of push the envelope. The idea of clinicians utilizing when they think, "Hey, this is a right way to go, getting new information." The fact that beta-blockers, Propranolol, first approved in 1968 Inderal for hypertension, we now know beta blockers are good for the treatment of congestive heart failure. That use initially was off-label.

There are certain patient populations, especially like pediatrics, that there're so little data available that if we don't use drugs off-label we are going to end up with a very small number of choices. And that goes for other issues like pregnancy and the very old as well. For orphan disease states, these are diseases that impact less than two hundred thousand patients; there is no incentive for industry to come up with therapies for the management of these diseases. So off-label use has been really very good in helping to manage or identify treatments for these.

Now, the government has also made some changes to encourage orphan drug expansion in development, seven-year exclusive patent rights after the development of the drug, some other tax benefits, and things like that. But up until that point, off-label use is really the only way to be able to manage these diseases. Off-label use also minimizes the cost to industry to do all the studies in the regulatory process necessary that usually costs millions and millions of dollars. If industry then uses that money they just saved back to research and development, that's a good thing. If they don't, it's not such a good thing, but again a relative pro.

And then cons. We don't have the scrutiny, the scientific scrutiny, with off-label use as we do with labeled indications. Typically there are much less amount of data to evaluate both safety and efficacy. So we may be rolling the dice sometimes. These safety concerns are real. Some studies have demonstrated increased risk of adverse drug reactions and an increase in medical errors with using drugs off-label. So that is a potential

problem.

There is the potential of liability issues, which we're going to hear about later on today so I'm going to skip right over that. There are cost issues, especially oncology drugs, biotechnology drugs, medications which cost five, ten thousand dollars a month, is this something reasonable to do? I mean, as a society how much are we going to pay for cost? That's, I think, an important thing to keep in mind. Certainly not the only thing to keep in, but we need to keep that as a relative concern.

Then from a patient's perspective, is my insurance company going to reimburse this? Legislation in 1993 required oncology drugs, if data are available, to demonstrate off-label efficacy of a particular treatment insurance companies have to actually pay for some of these off-labeled, or as they like to call it, investigational uses. But again, some of the cons of off-label use.

So when I think about it in terms of kind of real life applications is what data are out there. What other therapies are known, what is the relative risk, and relative benefit of these, quote, unknown therapies? From the patient's perspective will the insurance pay for it? I think another very important point for clinicians when they use medication off-label is if there are issues reported and there's an online med watch program, it's very easy to do so we can start accumulating that information as well as collecting your own data. A few years ago one of my Pharm D residents, Asim Abu-Baker and I, wrote a paper looking at the relative very little information available for the use of medications that treat type 2 diabetes in kids. Twenty years ago, it wasn't an issue, but we're seeing ten year olds now with type 2 diabetes. There's only one, other than insulin, only one medication approved for the use of treatment of diabetes in kids and that's only age twelve and higher and that's metformin. So we did a literature search and published that data to at least let providers know what was available because we were getting these questions all the time at The Endocrine Group. One does use off-label use medication; I think it's reasonable to share that information good or bad with other people. Whether it be case reports or looking at your own databases, we've done this with a number of our medications and in our own practice because I think that's important to be able to get that information out to allow other people to potentially use the information to make informed choices.

We don't have time to go through these, but one of the points I

want to make is regarding the Solo Star or the Apidra Solo Star, a disposable pen that is indicated for use in type 1 diabetes patients over the age of four or in adult type 2 patients. So if this insulin device is used in a fourteen year old type 2 diabetes patient, that's considered off-labeled use. So again, it's no big deal. Other times we just need more information to determine whether or not, you know, does the risk outweigh any potential benefit.

In conclusion, off-label use is very common. I think we need better scrutiny to identify where our potential issues are. I think we need to have ways for policy makers to try to encourage more information becoming available; whether that means incentives to industry or whether that means regulation or maybe some of both, that may be seen or may be the point. I think utilizing the off-label use of medications is appropriate in certain situations. I think we need to keep in mind the potential dangers of that and always keep that risk to benefit ratio.

Thank you very much for your attention.