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TITLE: Drug-Drug Interactions Seen In Treatment for Hepatitis C

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- [Moderator] Today we are very fortunate to have Dr. Christine MacBrayne as our speaker. So a little bit about Dr. MacBrayne she is a pharmacist who graduated from the University of Colorado Skaggs School of Pharmacy and Pharmaceutical Sciences. Upon graduation Dr. MacBrayne pursued a post graduate year one residency at Children's Hospital of Colorado where she was able to devote time in the childhood Immunodeficiency Program Clinic, providing guidance to families of HIV infected children. Following completion of residency Dr. MacBrayne sought post doctoral fellowship training under the mentorship of Dr. Jennifer Kiser. Dr. MacBrayne's research interests are in hepatitis C and HIV pharmacology, which is perfect because today she's gonna talk to us about drug-drug interactions. Some brief housekeeping notes the speaker will be taking questions at the end of the webinar, so please hold your questions until then. We will unmute the lines at that time and open this session up for discussion. So without further adieu, Dr. MacBrayne, the microphone is all yours.

- [Dr. MacBrayne] Perfect, thank you so much for that introduction,

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so today we're gonna go through as we already mentioned, but drug-drug interactions seen in the treatment of hepatitis C.

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So I have nothing to disclose.

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Following the end of this presentation, I would like you to be able to specifically understand the following learning objectives which are to discuss recent developments in the treatment of hepatitis C infection, including protease inhibitors and other emerging therapies, recall clinically important adverse effects, contraindications and drug-drug interactions associated with medications used in the treatment of hepatitis C infection, as well as devise strategies for managing drug interactions with hepatitis C therapies.

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So just a little bit of background information on the evolution of hepatitis C treatment. So from the first agents in the early 1990s we've really come a long way. Today we're treating patients with all oral therapies, so no more injections and really is generally a lot more well-tolerated than they used to be. I think some important things to point out so the first agents that were directly active against the hepatitis C virus replication cycle were the hepatitis C protease inhibitors boceprevir and telaprevir, these were approved in 2011. When added to pegylated interferon and ribavirin these agents did produce about a 75% cure rate in treatment patients without cirrhosis. While these agents significantly increased the cure rate they had many shortcomings including long treatment durations, three times a day dosing, large pill burden, major toxicities, as well as multiple drug interactions. And they were actually only active against genotype one hepatitis C virus. At the end of 2013 though, there was a major

game changer with received regulatory approval. This drug which is known as sofosbuvir has essentially replaced the use of telaprevir and boceprevir. It's extremely potent agent which allows for shorter treatment duration, it has no hallmark toxicities, very few interactions and has one pill once a day. And so this is really the game changer that has then since involved a lot of our hepatitis C treatment.

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This next slide goes through all the currently approved and in late stages of clinical development agents that we use for the treatment of hepatitis C. And you can see there that we have boceprevir and telaprevir still listed there but they are scratched out because they are no longer used. The approved direct acting antiviral agents inhibit three specific steps in the hepatitis C life cycle. Including the NS3/4A protease enzymes, the NS5 proteins, and the NS5B polymerase. Inhibition of the NS3 protease prevents the cleavage of the replication complex responsible for formation of viral RNA. The NS5B enzyme is essential for hepatitis C replication and the NS5A encodes a protein that appears essential to the replication machinery of hepatitis C and is critical in assembly of new infectious viral particles.

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So just a few treatment generalities also for hepatitis C that I think are important to takeaway. But as with HIV we use combinations of drugs with different mechanisms of action to maximize suppression of viral replication. And the use of a single agent actually will result in rapid emergence of resistant viral strains. Treatment durations range anywhere from eight to 24 weeks. Most of them are about 12 week treatment durations. There are ongoing studies though looking to see if we can shorten these treatment durations. Several of our agents, and most of them these days, are co-formulated so patients are only having to take one pill, sometimes once a day. Ribavirin is still used in some situations to increase the likelihood of a cure. All of the treatments are well-tolerated compared to our older therapies of pegylated interferon. And cost to access the therapies may impact treatment choice. Especially depending on where patients live in various states.

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Hepatitis C treatment abbreviations I just include this include this slide for completion's sake, throughout the presentation I do have a lot of charts and things and I will use the three letter abbreviations for the medications and so I just wanted to make sure that we all understood what I was talking about. So I did include this just for completion's sake.

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Here we have the most common adverse effects that are associated with the various treatment options for hepatitis C. And I'm not gonna go through all of these, but I did want to point out that compared to interferon and ribavirin these treatments are very well-tolerated. I am not aware of any patients who have had to stop treatment because of adverse events with these newer treatment options. And as you can see here, I do have ribavirin listed in the combinations where ribavirin can be used and there are more side effects when ribavirin is used. The biggest adverse effect of ribavirin is really fatigue because of lower hemoglobin and its side effect is hemolytic anemia.

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We also have in this chart listed all the contraindications to these different regimens. And I think, I'm not gonna go through this either they're there for your reference, but important to realize also a lot of the contraindications, or some of 'em, have to do with the use of ribavirin as well. And then for others the potential for drug interactions which we're gonna talk about more today.

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So with that let's go into drug interactions and why they're important. So this slide just illustrates that you kind of have a compounding issue when patients are taking more medication. So more drugs equals a greater risk of interactions. It is important to know though that not all patients that receive interacting drugs will experience a clinically significant drug interaction. And then there's a lot of other factors including genetics, different concomitant disease states, that can contribute to the possibility that a patient will experience a drug interaction.

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So today I'm specifically gonna talk about the top 10 drug interactions that are really relevant with hepatitis C treatment, and I wanted to tell you how I came up with this list of the top 10 drug interactions. So there was a medical claims database, a study that was done by a group called Lauffenburger et al. and they evaluated 20 million enrollees across 100 US insurers. They found that about 50,000 of those enrollees were hepatitis C positive individuals, on average, those patients had 10 prescriptions per patient and that wasn't including the hepatitis C treatments that they would be receiving. So using this cohort I really went through and reviewed the interactions and medications that these patients were taking and I went through and figured out which ones were most commonly used, and which ones were used to treat comorbidities which were most often observed. Things that we would see in our everyday practice. And then we do have at least one interaction which kind of falls into that last bullet point which is more of a clinically important interaction, so regardless of the frequency of concomitant use. And before we get into this top 10 list and did just want to do a quick review of the pharmacology so that some of things that I go through we can make sure we all are on the same page with.

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So first, there's two types of drug-drug interactions. The first is a pharmacokinetic interaction and this results in a change in the serum or plasma levels of a drug. And you can have pharmacokinetic interactions at the level of absorption, distribution, metabolism, as well as elimination. The other type of drug interactions that we are concerned with are pharmacodynamic interactions. And these interactions don't have a change in the serum plasma levels of the drug, but can result in additive, synergistic, or antagonistic effects.

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So I know that everyone's probably very familiar with CYP enzymes but I just wanted to go through them one more time. So the majority of drugs that people take whether they're hepatitis C or other medications for other concomitant disease based are metabolized by CYP3A4, actually about 50% of the drugs out there are metabolized by CYP3A4. And then you can see CYP2D6, 2C, 1A2 are also players but

they are less common. We do have quite a bit of information on the CYP enzymes, they've been studied since about the 1950s and we know that enzymes can either be induced or inhibited. And so, if an enzyme is induced or inhibited by a medication it can impact the pharmacokinetics of drug substrates for those enzymes, which is why they're a big important thing for us to understand in the context of drug interactions.

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The other important thing to understand in the context of drug interactions are drug transporters. So these have not been studied as long, only since about the early '90s have we really started to understand the impacts that transporters play in drug interactions. This slide specifically illustrates the different transporters that are present in the liver, but it is important to know that some transporters are also found in the gut, in the kidneys, and other places as well. The interactions that occur at the level of transporters are no less important than the interactions that we see with our CYP enzymes. So we do have influx as well as eflux transporters but specifically for hepatitis C, I want to draw your attention to several of these transporters. The first is in green and it's the OATP1B1 so this is an uptake transporter and it's gonna take substances from the plasma and move them into the liver. And the other ones that I want to focus on specifically for hepatitis C are BCRP, which is in brown, as well as the P-gp which is in the light purple there. These are both efflux transporters. So they're gonna take your substance from the inside of a cell and then move it out. So similar to our CYP enzymes our transporters can be inhibited or induced, and again, we have an alteration in our pharmacokinetics of the drug based on these transporters being inhibited or induced.

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One other important thing to keep in mind for drug interactions is that we do have a range of concentrations that balances the desired effect with the undesired effects so our toxicities. We call this concentration range the therapeutic range for a drug. So we do have several intrinsic as well as extrinsic factors that can influence where an individual's plasma concentrations do fall in this range. So some of the intrinsic factors age, weight, height, genetics we can't alter. Some of the extrinsic factors though diet, smoking, alcohol as well as drug interactions we can have a role in and we can alter those factors for this range. So for this range we can see the desired effects as well as the toxicities, and interactions are less likely to result in an unfavorable outcome for drugs that have a wide therapeutic range. And luckily for us our current direct acting antivirals for the treatment of hepatitis C do have a wide therapeutic range. There would have to be a larger change in concentration to result in either a loss of virologic control and or more toxicities from that therapy. That is a good thing for hepatitis C treatment doesn't meant that they can't have drug interactions because we definitely do have some, but that is one bonus. On the other hand though some of the medications that we see used concomitantly with our drug acting antivirals in individuals with hepatitis C do have narrow therapeutic indexes and that's a smaller change in the actual concentration of that medication could have clinical consequences. We have to kind of think on both sides. So, now that I've gone through the quick review of our pharmacology let's get into our top 10 list.

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The first interaction, or number 10 on my list, is sofosbuvir and amiodarone. So there actually is labeling now from this interaction that says that there is serious and life-threatening cases of symptomatic bradycardia as well as one case of fatal cardiac arrest that has been reported with coadministration of amiodarone with either ledipasvir and sofosbuvir fixed-dose combination or with sofosbuvir in combination with another direct acting antiviral. So sofosbuvir is really the common denominator in these cases that we've seen. There was nine original cases which prompted this important drug warning, three of those were taking sofosbuvir/ledipasvir, five were on sofosbuvir/daclatasvir, and one was on simeprevir/sofosbuvir. And these cases did experience bradycardia, fatal cardiac arrest, and some require pacemaker insertion.

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The mechanism for this interaction with sofosbuvir and amiodarone is somewhat unclear. There has been some more recent research into this showing that it's unlikely a pharmacokinetic interaction it's more of a pharmacodynamic interaction, and that is because we don't see differences in either of the sofosbuvir or the amiodarone plasma concentration in guinea pigs or monkeys when given alone versus in combination. Which lets us more believe that it's a pharmacodynamic interaction. In vitro, as well as ex vivo, and animal studies suggest the mechanism is either due to inhibition of a calcium channel, or disrupted intracellular calcium handling. Sofosbuvir plus amiodarone primarily impacts the SA node automaticity with potential delayed AV node conduction at later time points. And there really is conflicting data on the contribution of our other direct acting antivirals with this specific interaction. And it's really due to the different concentrations of the direct acting antivirals that we see being used which is why there's conflicting data on the contributions of this interaction.

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Ultimately though from this interaction there is a recommendation to avoid amiodarone during the hepatitis C treatment if possible. And while we don't have a lot of patients who are being treated for hepatitis C who are also on amiodarone many of those who are on amiodarone can't come off for various reasons. So the current recommendation is that for patients who are taking amiodarone with no alternative, you have to have inpatient cardiac monitoring for the first 48 hours of your direct acting antiviral treatment and then daily heart rate monitoring for two weeks after that.

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The next interaction that we'll talk about, which is number nine, is our hormonal contraceptives. And this is a really important one to keep in mind because we do have an increasing number of young women of childbearing potential who have hepatitis C. So between 2011 and 2014 there has been approximately 22% increase in the number of young women of childbearing potential with hepatitis C. So we have many hormonal contraceptive options. We have oral options, patches, vaginal rings, progestin-containing injectables, as well as progestin-containing subdermal implant. So many options to choose from, I have crossed out the IUD there at the bottom. Not because it's not a good method of birth control, but because due to a local administration of drugs they usually don't participate in drug interactions, so less relevant.

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This is a chart that goes through the different interactions that we see between our different forms of contraceptives and our hepatitis C agents. So what we do know about the interaction potential with contraceptives and direct acting antivirals though is that all of our direct acting antivirals have at least been studied with one combined oral contraceptive product. And this table shows the route of metabolism and the effects on the direct acting antivirals on the PK of the ethinyl estradiol and the progestins that have been studied, as well as the clinical recommendations for use of your hormonal contraceptives with your direct acting antivirals. So you can see from this chart that grazoprevir/elbasvir, ledipasvir/sofosbuvir as well as sofosbuvir/velpatasvir do not significantly alter the PK of hormonal contraceptives and thus are safe for concomitant use. So we don't have any issues using those together. However, we do have an important consideration with PrOD which is paritaprevir boosted ritonavir, ombitasvir and dasabuvir in combination with our ethinyl estradiol. So PrOD was studied with three different contraceptive options with the three different contraceptive options. And you can see here that we have increases in the levels but the main thing that came out of these studies is that we do see LFT elevations from these. So the current recommendation is that we cannot use estrogen containing contraceptives while on PrOD. So it somewhat limits our choices to our progestin-only options and a lot of people don't necessarily like those. One question has also come up if a patient were to discontinue the hormonal contraceptives while on birth control, which may or may not be the safest thing, or maybe they were to switch to a different form of birth control how soon can you resume your estrogen containing oral contraceptive? And following treatment would need to wait about two weeks before we resume that due to the half-life of the drug, and getting out of the system, and the potential for these LFT elevations.

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Number eight on the list that I want to talk about today is our calcineurin inhibitors, so tacrolimus and cyclosporine. So just to orient you to this table when there is not a prior dose adjustment required for either of these medications you will see they're highlighted in green. If we do require a prior dose reduction for the use of either cyclosporine or tacrolimus it is highlighted in yellow. And the contraindications are shown in red. Unshaded or kind of the grayish color boxes indicates that no interaction is expected. But no formal interaction study has been performed. I think important to take-away from this slide is that for all direct acting antivirals even if no prior dose adjustment is needed, we must monitor immunosuppressant levels and titrate the dose as necessary. We also do know that PrOD increases cyclosporine and tacrolimus exposures but specific guidance is available on how to adjust immunosuppressant doses during PrOD treatment and these adjusted doses were successfully applied in a study titled CORAL-1 which included 34 patients receiving PrOD post-transplant. So while we do have an interaction and they're highlighted there in yellow we do know that we can successfully dose adjust to make this a safe combination. Cyclosporine though inhibits one of those transporters I was talking to you about earlier, OATP1B1 as well as cytochrome 3A thus grazoprevir exposures are increasing 15-fold of cyclosporine and this combination is contraindicated. And then previously as I already mentioned we must monitor immunosuppressant even if a prior dose adjustment is not necessary. And this is really important for two reasons, we do have data to indicate that just having hepatitis C in and of itself impairs our metabolism. So when hepatitis C replication is progressed and metabolism improves the patients may require higher doses of immunosuppression to achieve the same exposures as before the hepatitis C treatment. Second, this drug class specifically with immunosuppression in our calcineurin

inhibitors is one situation where there was a healthy volunteer drug interaction study conducted and it did not reliably reflect what occurred in patients who are receiving the drugs. And we saw this with the combination of sofosbuvir and cyclosporine based on healthy volunteers and everything was fine, but when they gave it to transplant patients the simeprevir exposures were 6-fold higher with cyclosporine. So this is an important population to keep in mind that our healthy volunteer studies may not be a true prediction of what's going to happen.

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Next, I wanted to talk to you about some of the antiretroviral agents, since we do have a number of the coinfecting patients who are treated for hepatitis C. Here I've listed several takeaway points for the use of HIV antiretroviral agents with our hepatitis C agents. The first is that elbasvir/grazoprevir is incompatible with efavirenz, etravirine, as well as our boosting agents so ritonavir. PrOD is incompatible with efavirenz, etravirine, and our boosting agents except for atazanavir. Ledipasvir and sofosbuvir is compatible with most of our antiretroviral agents. Tenofovir levels though are increased with TDF. And sofosbuvir/velpatasvir is incompatible with efavirenz and etravirine. And the tenofovir levels again are increased with TDF. It's really important if you have a coinfecting patient though to always check for potential interactions and I have put the link in here for the AASLD/IDSA Guidelines which has a great table kind of a stoplight approach is what I presented to you somewhat today of different drug interactions with all of our HIV agents as well as our hepatitis C direct acting antivirals.

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So going a little bit further into the interaction with ledipasvir/sofosbuvir and then tenofovir and seeing those increased tenofovir exposures. You can see from this graph we have broken it in to kind of two pieces and we have our NNRTIs on one side and then ritonavir boosted protease inhibitors on the other, and I really wanted to draw your attention to the very end where we have ledipasvir/sofosbuvir with darunavir and atazanavir and just the range of the tenofovir exposures with available safety data is highlighted in that orange box. And so the problem is that when a patient is on a boosting agent so ritonavir boosted protease inhibitor in combination with tenofovir those levels exceed the range where we actually have safety data. And we do know that high levels of tenofovir can be associated with some renal dysfunction and bone mineral density issues. That is one interaction that we are concerned about and the current guideline recommendation specifically is to avoid boosted regimens with tenofovir in combination with these in patients who have a creatinine clearance less than 60 mls per minute just to be safe.

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Looking a little bit further into that though can we potentially use TAF instead of TDF to avoid this interaction? And the answer is, yes. TAF is not a renal substrate for OAT1 which is actually the transporter that mediates the renal toxicity with TDF. And you can see here that intact TAF transits directly into the target cells, where it's intracellularly activated to tenofovir diphosphate, so we actually have a 90% lower circulating plasma tenofovir levels compared to TDF when given. So, we could potentially use TAF in this situation to avoid that interaction you have a coinfecting patient and need to treat them.

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I'm also not gonna walk all the way through this slide but I did want to put together some kind of guidance on the potential direct acting antiviral options based on a patient's antiretroviral therapy and their renal function. I could probably give you an entire nother lecture on renal dysfunction and some of our hepatitis C agents and that is confounded with our antiretroviral agents, so I thought this slide would be just helpful and useful but it kinda breaks it down based on the HIV regimen that you're gonna choose and whether or not they're gonna have tenofovir and if their creatinine clearance is greater than or less than 60 mls per minute and what you should do in that situation.

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All right, so moving on. Our next interaction that I wanted to talk about is statins, so these are also a very important interaction many, many patients are taking statins and so we do want to be cognizant about this interaction and statins also have both CYP as well as transporter mediated actions that we need to consider. So some of the direct acting antivirals inhibit the uptake transporter OATP1B1, as well as the efflux transporter BCRP and CYP3A and that will result in increased plasma concentrations of our statins. And the way that they studied these specific interactions we'll use pravastatin a lot for our OATP1B1 and they'll use this to predict the direct acting antivirals' effects on OATP1B1. If we see increased levels that means it's an OATP1B1 inhibitor. Rosuvastatin is used in these studies then to look for our BCRP, because it is both a substrate for OATP1B1 as well as BCRP, but if we see increased levels we'll say that our direct acting antivirals is a BCRP inhibitor. And then similar to our immunosuppression I think it's always important to check for interactions with our statins as well as our direct acting antivirals.

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So this table shows the effects of the direct acting antivirals on the statin pharmacokinetics as well as provides the doses recommendations on concomitant use. And I think it's important because for several of these we have a max dose that we should be using, specifically looking at rosuvastatin and one for atorvastatin. So as I mentioned dose reductions are recommended, or required, with all of direct acting antivirals and there are contraindications with several of our statins if taken concomitantly with PrOD. Pravastatin and rosuvastatin can be used with appropriate dose reductions with all of the direct acting antivirals, however, I do want to point out that the use of rosuvastatin with ledipasvir/sofosbuvir is technically not recommended per the prescribing information. However, this is based off a drug interaction study with rosuvastatin ledipasvir and an investigational hepatitis C protease inhibitor and the large increase in the rosuvastatin exposures that were seen were more likely due to hepatitis C protease inhibitor and not the ledipasvir component. Ledipasvir is an inhibitor of BCRP so we know there is some interaction potential, but its effect on rosuvastatin is likely very similar to that of elbasvir's effect on rosuvastatin. And I just wanted to point that out because I don't have it listed as a contraindication here in this chart based on that data and that information.

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One other question that sometimes comes up is if we are going to start a patient on hepatitis C treatment should we discontinue the statin while they're on this treatment? And there was information

extracted from a Veterans Affairs HIV and Hepatitis C Clinical Case Registry they looked at approximately 6,000 coinfecting individuals and they saw that statin use was significantly protective of cirrhosis for patients with ALT of 40 or less. And for every 30% increase in time on the statin, there was a 32% decrease in the risk of developing cirrhosis. And diabetes and a low HDL were significantly associated with cirrhosis in patients with ALT greater than 40. So our statins do provide good benefit and the current recommendation is not to discontinue them while on treatment we can just dose adjust to appropriately make sure that we are not causing drug interactions.

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The next interaction I wanted to talk to you about is our antihypertensives agents about 40% of patients in that Lauffenburger study had hypertension and were being treated with some kind of agent. So just a few generalities CYP enzymes are not involved in the metabolism of our ACE inhibitors or our diuretics. So that lowers the chances that we potentially could have a drug interaction. Carvedilol and nebivolol are metabolized to some extent by CYP3A4. The contributions of CYP3A to irbesartan and losartan, there is some. And then calcium channel blockers are highly reliant on CYP3A for metabolism. So we do need to watch those potential interactions.

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Again, we have a chart here that kind of outlines the interactions that we may see and if they're safe to coadminister. And I specifically chose the antihypertensives that were most commonly used in this Lauffenburger study. So you can see that hydrochlorothiazide, lisinopril, and metoprolol should not interact. So we're safe to give those regardless of the hepatitis C regimen. There is a 42% increase in the turoso furosemide though with PrOD and that's due to the inhibition of UDP 1A1. So, should consider reducing the furosemide dose by half if coadministered. Amlodipine does not require a prior dose reduction with elbasvir/grazoprevir, ledipasvir/sofosbuvir, or sofosbuvir/velpatasvir but exposures are increased 2.6 fold with PrOD so that's again the dose should likely be reduced and monitoring is required during hepatitis C treatment.

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All right, now moving into our benzodiazepines, anxiolytics and sedative hypnotics. Again, about 24% of the patients in the Lauffenburger study were taking either zolpidem or benzodiazepines. So a big enough number that I thought it was an important drug interaction to look further into. There have also been two separate retrospective studies that found that about 40% of hepatitis C infected patients have anxiety disorders. And there's also a Dutch nationwide survey showing that benzos are among the drug most frequently used by hepatitis C infected patients. So again, a more commonly used medication that we need to consider the potential interactions for. Fortunately though zolpidem and benzodiazepines do not appear to be problematic with our hepatitis C treatments. So a dose reduction of alprazolam and increased monitoring with lorazepam and diazepam may be warranted if you're wanting to use PrOD. Due to some slightly increased levels specifically with alprazolam and PrOD.

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And number three is our gastric acid modifiers. So these are more important specifically for ledipasvir and velpatasvir and that is because the absorption of both of these agents is pH dependent. So there is some conflicting data from retrospective studies on whether proton pump inhibitor use compromises our SVR rates with ledipasvir and sofosbuvir. There was an HCV-TARGET trial that showed that the odds of an SVR in individuals not receiving a PPI were 2.47 times those individuals who were taking a PPI. Alternatively though, the HCV TRIO study showed that once daily PPI use was not predictive of SVR. They did see a potential signal with twice daily PPI use in univariate analysis but once they propensity matched the subjects this was not actually detected. So ultimately though it's safest to operate under the assumption that the proton pump inhibitors could reduce the chance for cure if not used properly.

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So here's some recommendations not only for proton pump inhibitors but some of our other gastric acid modifiers on how to appropriately take them. Recommendations for antacids and the H₂-receptor antagonists are the same for both ledipasvir and velpatasvir. For antacids, for both of those, we want to separate administration by four hours. In regards to our H₂-receptor antagonists they may be administered simultaneously with, or 12 hours apart, from sofosbuvir/ledipasvir or sofosbuvir/velpatasvir at doses that do not exceed doses comparable to famotidine 40 milligrams twice daily. And then, for proton pump inhibitors we do not want to exceed the proton pump inhibitor dose comparable to omeprazole 20 milligrams. And I do have a chart here in the corner that lists what those comparable doses are.

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One other really important thing to point out with proton pump inhibitors and dosing is that the recommendations are different for ledipasvir/sofosbuvir and sofosbuvir/velpatasvir. So it could easily confuse and I think it's just important to remind your patients several times of what the correct dosing is specifically for ledipasvir/sofosbuvir you're supposed to administer the 20 milligrams omeprazole equivalent simultaneously with sofosbuvir/ledipasvir under fasted conditions. On the other though for sofosbuvir/velpatasvir you're supposed to take it with food four hours before the 20 milligram omeprazole equivalent. So again, they are different, and if a PPI must be used there are specific instructions that regard to timing and administration with each of these agents.

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All right, number two is our antidepressants. So depressive disorders are seen in up to about 50% of hepatitis C infected patients. This table does show the most commonly used antidepressant medications from that Lauffenburger study. Most of these medications are not expected to interact with our direct acting antivirals the exceptions to that though are trazodone, which should be reduced if coadministered with PrOD. And then patients on bupropion, sertraline and venlafaxine are gonna require more frequent monitoring if used with PrOD and potentially a dose reduction. The go-to SSRI, or serotonin re-uptake inhibitors, during hepatitis C treatment is escitalopram and this does not interact with any of our commonly used direct acting antiviral treatment options. That is a safe one to use.

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For completeness' sake I also wanted to include direct acting antiviral interactions with our antipsychotics. These were not frequently used in the Lauffenburger study but there was a separate study that found that about 10% of patients were taking antipsychotics. I did just want to include this though for completeness' sake, this table came out of a recent review on psychotropic medications with direct acting antivirals interactions. And you'll notice that many of the commonly used antipsychotics like quetiapine, olanzapine and risperidone either contraindicated or caution is warranted if they are to be coadministered.

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And our number one drug interaction that I wanted to discuss today is opioid as well as opioid substitutes. You can see we do have from that Lauffenburger study the frequency of use is somewhat high, so specifically for hydrocodone 34% of patients were taking hydrocodone. Overall there is a lot of green on this chart meaning they're safe to coadminister. We also have some yellow with PrOD which means to monitor, and specifically for hydromorphone and oxycodone these are coded as yellow which means monitor and potentially a dose reduction is necessary. And that has more to do with the pharmacokinetics of these agents is altered in advanced liver disease. Depending on your patient's level of liver disease you may or may not need to dose adjust but it's always important to monitor. And that is the end of our top 10 list

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but I did also just want to point out really quickly an interaction just from last month a new case report that was published regarding concomitant use of warfarin and PrOD. And so this is a 58 year old male who once he initiated PrOD had subtherapeutic INR used to monitor the warfarin. He did require 125% total increase in the weekly warfarin dose to re-achieve a therapeutic INR while on his PrOD. And following completion of PrOD, the INR then became higher, so supratherapeutic. So this interaction has been seen in patients who are taking ritonavir as part of an HIV regimen making ritonavir more likely the culprit, but still something to think about and still needs a little bit more investigation as to what actually caused this interaction in this case report.

[00:40:04]

I wanted to direct you to some resources for drug interactions because I also cannot remember all the drug interactions that we went over today so I also don't expect you to remember them. But there are some really great resources out there that you can use. This first one is the University of Liverpool and I have the website listed there, and it's a great reference. You plug in your concomitant medications with your hepatitis C treatment you want to use and it will give you a stoplight approach. It will also give you studies that were used as well as predict a potential interaction if that study hasn't been done based on the pharmacology of each of these agents. We also have antiretroviral specific guidelines if you have a patient who has coinfection with HIV and so again I have the AASLD/IDSA Guidelines listed here and then DHHS the HIV specific guidelines also has some good recommendations on drug interactions. And I think just in the interest of time I will stop there and open it up to questions. I did have a patient case though if anyone wants to go through it and just kind of see how I approach drug interactions.

- [Moderator] Dr. MacBrayne I think we're interested in hearing your case.

- [Dr. MacBrayne] Oh perfect, okay, then we'll go through it.

- [Moderator] Thank you.

[00:41:24]

[Dr. MacBrayne] So this our case so it's a 64 year old Caucasian female. History of injection drug use, history of hypertension, hyperlipidemia, GERD and depression.

[00:41:38]

This patient does have hepatitis C genotype 1a and they are considered treatment experienced based on the fact that they were treated with peg-interferon and ribavirin five years ago, but stopped after three months due to a severe skin reaction and incomplete response. Their most recent hepatitis C RNA is listed there. They also had a liver biopsy approximately one month ago that showed grade two inflammation, as well as stage four fibrosis.

[00:42:08]

This is the patient's clinical labs so you can see ALT and AST are 32 and 30 respectively. Serum creatinine is 1.07 which ultimately ends up being a creatinine clearance of about 119 mls per minute. And as I mentioned previously this is really something that's important to keep in mind because some of our hepatitis C regimens do require modifications in certain renal impairments. You can also see we have white blood cell, ANC and platelets listed there.

[00:42:41]

Her current medications for her hyperlipidemia she's taking rosuvastatin 20 milligrams once a day. Hypertension, lisinopril 20 milligrams once a day, amlodipine five milligrams once a day. For her GERD she's taking omeprazole 40 milligrams once a day. Depression, venlafaxine 75 milligrams once a day. And she has no known drug allergies. So that kind of leaves us with what hepatitis C regimen are we gonna choose for this patient?

[00:43:11]

And you can see here I have listed the hepatitis C treatment options across the top, as well as her concomitant medications down the side. And regardless which regimen you choose for her hepatitis C treatment we're gonna have to make some modifications. So we're gonna have to do something to all of them, which I think is an important point to take away from this case.

[00:43:35]

There was also some questions that have come up before and there was a really good poster presentation at the international workshop on clinical pharmacology for HIV and hepatitis therapies about when to restart amlodipine after PrOD. If we go back here you can see that if we were to coadminister amlodipine and PrOD that there is a 2.6 fold increase and we might need to consider a dose reduction. So when can you restart someone on their full dose of amlodipine? So this was a PB-PK

model developed that linked the drug concentrations to blood pressure measurements. Following completion of PrOD they did note that the amlodipine PK took about five days to resolve. But on the other hand the average systolic blood pressure was only three millimeters per mercury lower if the amlodipine dose was escalated immediately. So ultimately it doesn't really matter, you can choose to wait those five days till the amlodipine's out of their system or you can start right away for that recommendation.

[00:44:37]

But going back to our patient looking at each of the different regimens, I have listed out here what we would want to do for this patient if we chose each of these regimens. So if we chose sofosbuvir/ledipasvir we're gonna have to decrease her omeprazole to 20 milligrams from 40 and make sure to counsel her appropriately on how to take them simultaneously. We're also gonna have to decrease her rosuvastatin to 10 milligrams from 20 because that is the max recommended dose. Monitor lisinopril and amlodipine toxicities. And we don't need to do anything with her venlafaxine. And important for all patients, regardless of the regimen we choose, we're gonna make sure to educate the patient not to take any new medications whether they're prescription, over the counter, dietary, or recreational without consulting us so that we can make sure it's done safely.

[00:45:28]

If we were to start the patient on sofosbuvir/velpatasvir, again, we're gonna have to decrease omeprazole to 20 milligrams, decrease the rosuvastatin to 10, no changes to venlafaxine, but we are gonna have to monitor amlodipine.

[00:45:43]

If we choose to start elbasvir/grazoprevir we will have to decrease her rosuvastatin to 10 milligrams once a day, monitor amlodipine, but we don't have to do anything to the omeprazole, lisinopril, or venlafaxine.

[00:45:57]

And last if we want to use PrOD for this patient we're going to have to decrease the rosuvastatin to 10 milligrams, monitor for toxicities related to venlafaxine and reduce the dose if clinically indicated, monitor for amlodipine, and no changes to either her omeprazole or lisinopril.

[00:46:17]

So just quickly in summary, an important consideration in the treatment of hepatitis C is the potential for drug interactions. In general, current therapies have well-characterized pharmacology and manageable drug interaction profiles. And a systemic approach for identification and management of drug interactions is essential.

[00:46:36]

And with that I will now open it up to any questions.

- [Man] Christine this is Daniel Fierer I've got a question if you would?

- [Dr. MacBrayne] Yeah.

- [Daniel] Hi, thanks for talking. In the package insert for the SOF/VEL, the Epclusa brand, they had an interesting, and it kind of worried me, mentioned here at the very top of page 13, which I don't expect you to have in front of you, about the solubility. And this is distinctly different than the ledipasvir solubility and concerned me about the gastric PH issue because it's practically insoluble above PH five, slightly soluble at PH two, and soluble at PH 1.2. So PH 1.2 is basically active after the meal but even at PH two it's a log, you lose a log of solubility. Now just 3.6 milligrams per ml and I didn't crunch that to see if that would be adequate though for getting the dose absorbed sufficiently. But it was a significant concern given the fine theoretically about acid suppression but that solubility there seems to me that you pretty much need to have no gastric acid suppression whatsoever.

- [Dr. MacBrayne] Right. - [Daniel] Absorption there and you're not PPI possibly or with meals, so I've been telling, I've devised my language I find that everyone knows how to eat dessert and so I tell them to take the pill after a meal as if for dessert. Because I get all kinds of questions about what do you mean by after a meal? And I say eat it like dessert, everyone knows that.

- [Dr. MacBrayne] Yeah and I think that's really important is like right after—

- [Daniel] 'Cause they say with the meal and I just don't agree with that. It's just not enough time to generate the gastric acidity if you really want to be safe. I'm quite concerned about this drug, compared to harvoni and this looks much less soluble and much more acid dependent than harvoni velpatasvir more than ledipasvir. Significantly so, not just a little bit.

- [Dr. MacBrayne] Yeah and I do know before the drug got brought to market that was definitely one of the biggest concerns that they had, and they still were able to bring it to market kind of with the recommendations that we went over today to take it with food. But I agree with you it does have very, very poor solubility and really digging into those recommendations we have to make sure we really are telling our patients the very, very most opportune time to take it to make sure we're at least getting the most in that we can.

- [Daniel] But I mean a PPI 22 hours later gastric PH aside it's just not that hard to achieve on proton plus inhibitor. And so, I mean even 24 hours after a dose, even when you eat something, I wonder if there are any data looking at the gastric PH?

- [Dr. MacBrayne] I personally haven't seen any data specifically on that and gastric PH so many hours after. But based on the mechanism of how PPIs work I mean exactly what you're saying makes sense, because we're essentially shutting off those pumps and so you still could have a higher PH even 22, 23 hours—

- [Daniel] Insoluble at PH five, I mean those are, anyway that's my concern about the drug. Thank you

. - [Dr. MacBrayne] I agree, so if we can make it so people don't have to take the PPI especially with SOF/VEL I think that's probably our best option.

- [Moderator] Dr. MacBrayne just to follow-up on Dr. Fierer's comment about the solubility and also on Epclusa, I've noticed that a fair number of my patients have been reporting really bad heartburn, like a

recurrence of heartburn or worsening of heartburn symptoms on the Eplusa and we obviously tell them try to avoid any acid suppression as much as possible. But in situations where sort of the symptoms become recalcitrant what can we do while the patient's on treatment to help, to ensure that the Eplusa's still soluble but at the same time relieves patient's symptoms?

- [Dr. MacBrayne] Right, so just from clinical practice what I've see more commonly is the use of some of our just antacids, Tums and some of those things, because they don't have quite as profound effects on the gastric PH as like a PPI. And then also just some of the recommendations of trying not to eat spicy foods and those things, don't drink acidic drinks, and some of the more non pharmacologic things we can do to prevent it. While I know a lot of times in this patient population those don't work, I think it is just important to try to re-educate them on some of those things too in case it might be some dietary things that could be contributing.

- [Moderator] Thank you. Do we have any other questions from our listeners on the line? Anyone who wants to type in a question? I have another sort of anecdotal question Dr. MacBrayne. For our seizure patients I've noticed that sort of phenytoin and phenobarbital are relatively contraindicated in the sofosbuvir-based treatment regimens at least, should we, we're referring them over to neurology to see if the patient can be switched, but in certain cases it's really hard to get them to neurology or it's really hard to get them to be seen, or switched, in a relatively reasonable time period. So what can we do during those instances where the patient's on phenytoin do we just hold off on the medication or are there other regimens that we can consider?

- [Dr. MacBrayne] Yes, I think that's an important question. I didn't actually bring up a lot of the seizure stuff today but exactly as you were saying some of the older seizure meds phenytoin, phenobarbital, valproic acid are the ones that we really see these interactions with. Some of our newer ones keppra and lacosamide don't have as many interactions and so a lot of times the neurologist will successfully switch them but like you said we can't always incorporate that in a timely manner. So I think that, at least what I've seen done, in clinical practice is maybe if they can't see a neurologist at least have someone know that you're going to try to do that, a lot of people will hold off until they can actually get the antiepileptic switched over and make sure that someone stable on their new regimen just because of the risk of having someone start having seizures because their levels are too low or toxicity on the other end, none of those older medications have super great side effect profiles so it kind of is up to you and your practice. I personally would probably say try to wait and or if you can't get them in to see neurology at least see if you can speak with the neurologist and see what their best recommendation would be.

- [Moderator] Thank you everyone for attending the HepCure Tele-Education webinar this afternoon. Thank you Dr. MacBrayne.

[Video End]