The Clinical Use of Fixed-Dose OADs

Our guest author is Clare J. Lee, MD, MHS from the Johns Hopkins University School of Medicine in Baltimore, Maryland.

After participating in this activity, the participant will demonstrate the ability to:
- Describe the rationale for fixed-dose combination oral antidiabetic drugs.
- Evaluate the efficacy, tolerability, cost, and adherence factors related to fixed-dose combination OADs.
- Identify how fixed-dose combinations can be used to tailor oral diabetes therapy.

This discussion, offered as a downloadable audio file and companion transcript, covers the important topic of fixed-dose oral antidiabetic drugs. This program is a follow up to the eDiabetes Review newsletter—The Current State of Fixed-Dose OADs.

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Clare J. Lee, MD, MHS has indicated that there will be no references to unlabeled/unapproved uses of drugs or products.

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Faculty Disclosure
Clare J. Lee, MD, MHS has indicated that she has no financial interests or relationships with a commercial entity whose products or services are relevant to the content of this presentation.

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BOB BUSKER: Welcome to this eDiabetes Review Podcast.

Today’s program looks at how the information in our recent newsletter on Fixed-Dose Oral Combination Agents can impact clinical practice. Our guest today is that newsletter issue’s author, Dr. Clare Lee, assistant professor of medicine in the Division of Endocrinology, Diabetes & Metabolism at the Johns Hopkins University School of Medicine.

eDiabetes Review is jointly presented by the Johns Hopkins University School of Medicine, and the Institute for Johns Hopkins Nursing. This program is supported by educational grants from AstraZeneca and Merck.

Learning objectives for this audio program include:
- Describe the rationale for fixed-dose combination oral antidiabetic drugs.
- Evaluate the efficacy, tolerability, cost, and adherence factors related to fixed-dose combination OADs.
- Identify how fixed-dose combinations can be used to tailor oral diabetes therapy.

Dr. Lee has indicated that she has no financial interests or relationships with any commercial entity whose products or services are relevant to the content of this presentation. Her discussion today will not reference the unlabeled or unapproved uses of any drugs or products.

I’m Bob Busker, managing editor of eDiabetes Review. Dr. Lee, thank you for joining us today.

DR. CLARE J. LEE: Thank you for having me. It’s a great pleasure.

MR. BUSKER: FDC OADs — fixed dose combination oral antidiabetic drugs. Your newsletter issue provided a lot of information to help clinicians better use these agents to improve glycemic control, reduce the potential for side effects, and even achieve better adherence. Today we want to focus on what that information can mean in clinical practice. So start us out, if you would please doctor, with a patient scenario.

DR. LEE: Ms. Jones is a 57 year old school bus driver whose type 2 diabetes was diagnosed three months ago during a routine screen at your primary care clinic. She has a history of hypertension and obesity with a body mass index of 32. The A1c at that time of her diagnosis was 9.6%. She has since met with the nutritionist and started a low carbohydrate diet. She has also increased her physical activity by joining a gym and attending group aerobic exercise class twice a week. Her repeat A1c is 9% during today’s follow-up visit. She is anxious to improve her glycemic control.

MR. BUSKER: A newly diagnosed type 2. She’s obese, she’s hypertensive. But she’s made a commitment to diet and exercise. Even with that, she’s not under control. What would be your initial recommendation for this patient?

DR. LEE: She’s made great strides in emphasizing her lifestyle as the cornerstone of her type 2 diabetes treatment. I definitely congratulate her for doing so and continue to encourage her to make that a big, important commitment in her life. In addition, however, she will need a medication because her hemoglobin-A1c today is 9% despite her making some changes in her diet and exercise routine.

Typically we would start metformin as the first treatment of choice, and there is unanimous agreement about metformin as the first line unless there is a contraindication. Another option is to start a medication such as a combination drug containing metformin plus another medication such as a DPP4 inhibitor, or a combination of metformin plus SGLT-2 inhibitor, metformin plus sulfonylurea, or even metformin combined with TZD. Once you start one of these medications, the important thing is repeat her hemoglobin-A1c within three months to reevaluate the impact of the new medical therapy.

MR. BUSKER: Initiating with metformin, which is directly in line with the guidance, or initiating with metformin plus another agent: what’s the rationale for the latter?

DR. LEE: The typical recommendation from a variety of professional organizations would be a stepwise approach where you start first with lifestyle and then add metformin. Then if the A1c goal has not been reached, add another medication on top of that.

However, primary care physicians face some challenges face with this stepwise approach.
One is that there might be some slowness in the up-titration process, related to perhaps the patient follow-up speed or some level of clinical inertia where the physician wants to maximize the dose of the first medication before adding a new one.

Because of the variety of these scenarios, the up-titration of medications to achieve the goal of hemoglobin-A1c can be diminished. One approach to overcome these challenges would be to start right away with a combination pill that would contain two medications to treat type 2 diabetes.

MR. BUSKER: Continue that thought, please, doctor. What are the pros and cons of fixed-dose combinations vs just prescribing the two agents individually?

DR. LEE: The big advantage of starting a combination medication is the possibility of avoiding the side effects related to the individual medication, mainly by avoiding the maximum dose of each medication. You have the option of starting a lower dose of one drug combined with a lower dose of another drug, rather than maximizing drug number one then adding drug number two.

The other benefit is a greater glucose lowering efficacy of simply using two agents instead of one, and this could be encouraging both for the provider and the patient in up-titrating medications to ultimately achieve the hemoglobin A1c goal.

On the other hand, we need to think about some cons. The combination drugs might cost more, depending on the patient’s insurance situation. And if a side effect is associated with starting a combination drug, you might not be sure which medication included in the combination pill could be causing the side effect. So those are some of the concerns a provider should keep in mind.

MR. BUSKER: That first negative you mentioned — higher cost. That was addressed in one of the articles you reviewed in your newsletter.

DR. LEE: As I mentioned, the prescription costs could be higher with fixed-dose combination medications. Lokhandwala and colleagues analyzed cost and found that the monthly prescription costs for a fixed dose combination drug was $290 compared to $225 with the equivalent loose medications.\(^1\) What’s interesting, however, is that all-cause monthly costs were lower in the fixed dose combination cohort compared to loose-dose combination cohorts, suggesting there might be some savings beyond the monthly prescription cost.

MR. BUSKER: The fixed-dose combinations that contain metformin — what side effects do clinicians need to consider?

DR. LEE: Several combinations contain metformin as one of the two medications in these fixed-dose combination pills. The first, a metformin/DPP4 inhibitor, has gastrointestinal side effects (which will be the case for all fixed-dose combination pills containing metformin). The DPP4 inhibitor can also cause GI side effects, but they are usually mild, and overall the side effect profile of DPP4 inhibitors is relatively benign.

Next is a metformin/SGLT-2 inhibitor combination, which, in addition to GI side effects, can cause an increased risk of genitourinary infection. That side effect would be associated with what we already know about SGLT-2 inhibitors. This combination can be helpful for patients who would benefit from weight loss because both metformin and SGLT-2 inhibitors can cause modest weight loss. In addition, there might be some benefits with hypertension management, because the SGLT-2 inhibitor has that property. So you can certainly think of this combination for patients with weight issues or hypertension.

Next we can consider metformin/sulfonylurea. Again, the side effect profile is basically what we know of each individual medication, GI side effects, weight gain, and higher risk of hypoglycemia, probably because of the sulfonylurea.

Next, metformin/TZD, which together can cause a little weight gain, probably related to TZD. This combination is also associated with possible cardiovascular risk, bone loss, and bladder cancer risk that have been associated with the TZD class.

MR. BUSKER: What about the efficacy of these various fixed-dose combinations?

DR. LEE: That’s a great question. In general, the efficacy of these combination pills would be roughly equivalent to the combined efficacy of each individual medication. But some studies included in the newsletter specifically mention the A1c reduction...
power of these combination pills. For example, a DPP4 inhibitor and metformin combination, specifically sitagliptin and metformin, can reduce the A1c by 2.4%. Similarly, saxagliptin and metformin can reduce A1c by 2.5%, assuming you can titrate the dose to the maximum for each ingredient.

For the other combination medications such as TZD and metformin, the papers in the newsletter show no specific A1c reduction capacity.

MR. BUSKER: I want to bring up the concept of pill burden and how that relates to adherence. It makes logical sense — and some of the articles in your newsletter issue provided evidence of this — that the more you can simplify the treatment regimen, the greater impact it’s going to have on adherence. A fixed-dose combination means fewer pills the patient has to remember to take. That simplifies the regimen, as does once-daily dosing. Which of the fixed-dose combinations that contain metformin can be taken once daily?

DR. LEE: At least three types of combination pills allow once daily dosing and contain metformin extended release: saxagliptin/metformin XR, sitagliptin/metformin XR, and pioglitazone/metformin XR. These are great tools to keep in mind to streamline our patients’ medication regimens to ultimately improve their medication adherence.

MR. BUSKER: Thank you. And we’ll return with Dr. Clare Lee from Johns Hopkins in just a moment.

SUSAN PORTER: Hello. I’m Susan Porter, clinical nurse practitioner and certified diabetes educator at the Johns Hopkins University School of Medicine. I’m one of the program directors of eDiabetes Review.

If you found us on iTunes or on the web, please be sure to subscribe. This podcast is part of Johns Hopkins eDiabetes Review, a new educational program providing monthly activities certified for CME credit and nursing contact hours, with expert commentary and useful practice information for clinicians treating patients with type 2 diabetes.

For additional information, or to subscribe to receive our newsletters and podcasts without charge, please visit www.ediabetesreview.org. Thank you.
**MR. BUSKER:** What should the clinician consider when selecting an alternative therapy to metformin?

**DR. LEE:** Before switching his medication regimen, you want to examine some clinical factors that could play a role: namely, is there a lifestyle nonadherence? Is there weight gain and perhaps worsened insulin resistance? Could there be a decline in pancreatic function? Chances are, a combination of all of these factors is playing a role in the progression of his diabetes. So in selecting a medication that could help him in addition to optimizing his lifestyle, you’ll think of medications that won’t cause gastrointestinal side effects, which is the most common side effect experience in metformin users. That’s what bothered him with metformin, so the idea would be to find a medication to help with his diabetes without causing GI side effects.

One medication in particular could cause GI side effects is a GLP1 agonist, which we won’t discuss much here because it’s an injectable and isn’t available as a combination mediation. DPP4 inhibitors also have some gastrointestinal side effects but they are rather mild in side effects overall, so a DPP4 might be a fair one to consider in this gentleman. SGLT-2 inhibitors, sulfonylurea, and TZDs will also be in consideration for this gentleman.

**MR. BUSKER:** What would prompt you to use a fixed dose combination pill instead of simply switching to monotherapy with a different agent?

**DR. LEE:** Because his A1c is 8.9% and assuming he is doing his best with his lifestyle, chances are we won’t be able to bring his A1c down to his goal, which is usually around 7% with monotherapy, so he will probably require more than one medication. If we were to follow the usual stepwise approach, we would start him on one medication, maximize the dose as much as he can tolerate, then add the second agent. But perhaps another approach that could both speed up the up-titration of medications and increase adherence overall to medications would be one of these combination pills.

**MR. BUSKER:** What fixed dose combinations that do not contain metformin and also allow for once daily dosing are currently available?

**DR. LEE:** We have three combinations: first, DPP4 inhibitor/SGLT-2 inhibitor; second, DPP4 inhibitor/TZD; and third, TZD/sulfonylurea. These three combinations are once-daily dosing and do not contain metformin, and they could be certainly considered for treatment of diabetes in our gentleman.

**MR. BUSKER:** Thank you for that case and discussion, Dr. Lee. Let me ask you to bring us one more patient scenario.

**DR. LEE:** Ms. Klein is a 76 year old woman with longstanding type 2 diabetes, moderate chronic kidney disease that is phase 3 with a GFR of 40, coronary artery disease status post stents, and prior pulmonary embolism now on lifelong anticoagulation. Among her 12 medications, two are glucose lowering drugs, glipizide and linagliptin. She has had severe hypoglycemia on occasion, requiring assistance. Her most recent HbA1c was 8.4%.

**MR. BUSKER:** Elderly lady with kidney and CVD problems, plus some severe hypoglycemia. She’s taking a dozen pills a day, and her A1c is too high. How would you address managing this patient?

**DR. LEE:** She symbolizes a complex clinical situation of multiple comorbidities with diabetes that is not at goal, and she’s having hypoglycemia on top of that. So it becomes a clinical challenge, and we need to think carefully about her medical therapy. Foremost, we need to review her lifestyle, her life circumstance, to provide the best set of recommendations. In particular, I would ask if she’s living alone or with someone to understand the risk of hypoglycemia and think about the interactions among her 12 medications and whether all those 12 medications are warranted to avoid polypharmacy and possibly cause side effects and harm.

After we understand those factors, we will focus on how to improve her diabetes. One thing I would be concerned about, given her age and her history of severe hypoglycemia, is to find diabetes therapies that will not cause hypoglycemia. She is currently taking glipizide, a medication that increases her chances of hypoglycemia. So given her circumstance, I would be inclined to stop that medication to reduce her chances of developing hypoglycemia in general.

Then the question becomes what other therapies we can consider once we stop the glipizide. Chances are, she may or may not need a combination drug, but
given her pill burden and her comorbidities, it might be helpful to consider a fixed-dose combination pill to address her diabetes management.

Right now, she’s only taking glipizide and linagliptin. If we discontinue glipizide, she would be taking linagliptin only. Linagliptin has an A1c reduction of up to 0.5% in general, so that alone may not help her reach her A1c goal, which I imagine would be around 7.5%, given her age and comorbidities. We would have to also think about some combination therapy for her diabetes to help her reach that A1c goal.

MR. BUSKER: You mentioned she has chronic kidney disease. That’s going to rule out metformin, and also the SGLT-2 inhibitors as options. Is that correct?

DR. LEE: That’s correct. Her medication choices will be limited by getting rid of metformin and an SGLT-2 inhibitor. We just mentioned that sulfonylurea may not be a good option for her either, given her elderly age and risk of hypoglycemia.

MR. BUSKER: Fixed dose combinations without metformin, without a sulfonylurea, and without an SGLT-2 inhibitor. What does that leave for suitable options for this patient?

DR. LEE: Of the several options of non-metformin-containing, fixed-dose combination medications, we’re left with a DPP4 inhibitor/TZD.

MR. BUSKER: Are there any other clinical considerations physicians need to be aware of in treating this patient?

DR. LEE: Yes. Realizing that she has a rather complex clinical situation and comorbidities, we need to be careful to avoid hypoglycemia and define an A1c goal that may be different than the usual 7% for the vast majority of patients with type 2 diabetes; her A1c goal may be higher. We want to make sure she’s self-monitoring blood glucose so it can be correlated with A1c values to make sure the A1c goals are correct, because the A1c can be falsely low in patients with CKD.

The other clinical concern we need to explore would be cost. Prescribing a fixed-dose combination medication for diabetes management could perhaps cost her a little more monthly, as we reviewed in one of the newsletter articles. But the increased cost could pay off in other ways if we can reduce her overall medical expenses by ultimately promoting improved health. In addition, fixed-dose combination pills can promote better adherence to medications, especially for a patient who has to take multiple medications, as does our patient.

So in the setting of chronic kidney disease, we may also need to use insulin to further optimize her diabetes control. However, fixed dose combination pills can decrease the need to use insulin or can delay the onset of insulin initiation.

MR. BUSKER: Thank you for today’s cases and discussion, doctor. Let’s wrap things up by reviewing what we’ve talked about today in light of our learning objectives. So to begin: the rationale for fixed dose combination oral drugs.

DR. LEE: Type 2 diabetes is a progressive disease that will require up-titration of medical therapy; and as we intensify the medical therapy, a fixed-dose combination medication can help us reduce the pill burden while improving overall adherence.

MR. BUSKER: And our second objective: the efficacy, tolerability, cost, and adherence related to fixed-dose combination OADs.

DR. LEE: The efficacy and tolerability of fixed-dose combinations are similar to those of the respective loose pill combinations, and the overall health care cost can potentially be lowered with fixed dose combination pills compared to that of loose pill combinations, possibly because of benefits beyond the actual prescription costs. Overall, simplifying the patient’s regimen can certainly promote better adherence, which is important.

MR. BUSKER: Finally: tailoring oral diabetes therapy with fixed-dose combinations.

DR. LEE: The main advantage of using fixed dose combination pills would be to go beyond the traditional stepwise approach and be able to up-titrate the medical therapy in a time efficient manner and also in a manner that may reduce the side effects associated with each individual medication. Fixed-dose combination pills may be associated with side effects similar to those with individual medications, so we need to consider the kidney function as well as
gastrointestinal side effects, as you would with each individual medication.

MR. BUSKER: Dr. Clare Lee from the Johns Hopkins University School of Medicine, thank you for participating in this eDiabetes Review Podcast.

DR. LEE: Thank you for the opportunity and I really enjoyed it, and I hope the audience did, as well.

MR. BUSKER: To receive CME credit for this activity, please take the post-test at www.ediabetesreview.org/test.

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