JOHNS HOPKINS MEDICINE eLITERATURE REVIEW

Jointly provided by the Johns Hopkins University School of Medicine and the Institute for Johns Hopkins Nursing

eDiabetes Review

Vol 3: Supported by educational grants from NovoNordisk, Sanofi, and Merck & Co., Inc.

VOLUME 3 - ISSUE 12

LISTEN TO PODCAST | DOWNLOAD PODCAST | PHYSICIAN POST-TEST | NURSE POST-TEST

In the Clinic: The New Ultralong-Acting Insulins

- Identify scenarios in which patients can benefit from ultralong-acting insulins.
- Discuss the potential negatives of ultralong-acting insulins.

Guest Faculty Disclosure
Dr. Gianchandani has disclosed that she has no financial interests or relationships with any commercial entity whose products or services are relevant to the content of this presentation.

Unlabeled/Unapproved Uses
Dr. Gianchandani has indicated that there will be no references to the unlabeled or unapproved uses of drugs or products.

MEET THE AUTHOR

Roma Gianchandani, MBBS
Clinical Associate Professor
University of Michigan
Ann Arbor, Michigan

Release Date:
October 11, 2018

Expiration Date:
October 10, 2020

LISTEN TO PODCAST NOW | DOWNLOAD PODCAST | SUBSCRIBE NOW | PHYSICIAN POST-TEST | NURSE POST-TEST

OTHER RESOURCES

Download the podcast transcript

Go to the companion newsletter

NEWSLETTER ARCHIVE | SHARE WITH A COLLEAGUE

PROGRAM DIRECTORS

Nestoras Mathioudakis, MD, MHS
Assistant Professor of Medicine
Clinical Director, Endocrinology, Diabetes & Metabolism
Johns Hopkins University School of Medicine
Baltimore, Maryland

Kathleen Dungan, MD, MPH
Associate Professor
Associate Division Director for Clinical Services
Division of Endocrinology, Diabetes and Metabolism
The Ohio State University
Columbus, Ohio

Susan Porter, MSN, CRNP, CDE
Clinical Nurse Practitioner and Certified Diabetes Educator
University of Maryland, St. Joseph Medical Group Owings Mills Internal Medicine
Baltimore, Maryland

Podcast Transcript

BOB BUSKER: Welcome to this *e*Diabetes Review podcast.

I'm Bob Busker, managing editor of *e*Diabetes Review. We're here today with Dr. Roma Gianchandani, Clinical Associate Professor at the University of Michigan in Ann Arbor, to talk about using ultralong-acting insulins in clinical practice.

***e*Diabetes 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 Merck & Co., Inc, NovoNordisk, and Sanofi.**

Learning objectives for this audio program include:

- **Identify scenarios in which patients can benefit from ultralong-acting insulins.**
- **Discuss the potential negatives of ultralong-acting insulins.**

Dr. Gianchandani 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. She has also indicated that there will be no

references to the unlabeled or unapproved uses of drugs or products.

MR. BUSKER: Dr. Gianchandani, thank you for joining us today.

DR. GIANCHANDANI: Thank you for inviting me to provide an update on this exciting field.

MR. BUSKER: Ultralong-acting insulins. In your recent newsletter issue, you gave us a full introduction to these newest glucose control formulations. I'd like to shift our focus to look at the potential uses of these agents in the clinic. So please start with a patient scenario.

DR. GIANCHANDANI: This is a 65-year-old male teacher who has a 20-year history of type 2 diabetes. His diabetes was well-controlled on maximum doses of metformin, linagliptin, and canagliflozin, until a year ago when his blood sugar started to rise. He intensified exercise and lifestyle behaviors but continues to have significant hyperglycemia through the day. His comorbidities include hypertension and hyperlipidemia. He has no allergies and on examination he has normal vital signs. He's 5'9" and weighs 120 kilos. He has mild neuropathy by monofilament testing only.

On labs his A1c is 8.2% with a fasting sugar of 201 mg/dL. His self-monitoring blood glucose reveals an average of 180 mg/dL to 200 mg/dL. At noon it is around 200 mg/dL, in the evening 160 mg/dL.

To improve his glycemia, we stopped the canagliflozin, which he finds very costly, and started glargine at 20 units and slowly titrated by a 2-0-2 method to 40 units at bedtime over four weeks. As this dose he is experiencing nocturnal hypoglycemia three days of the week at around 2 am, in the morning he's hyperglycemic in the 190s to 200s, and his blood sugar through the day is 140 mg/dL to 150 mg/dL preprandially.

MR. BUSKER: Why did you decide to switch this patient from orals to insulin? Aside from the cost of the canagliflozin, does this patient really need insulin?

DR. GIANCHANDANI: This patient has had diabetes for over 20 years. As the duration of diabetes increases, patients start losing some of their beta cell function, and this deterioration of function makes them insulin-dependent. Therefore, he may need insulin at that point. He is not controlled by noninsulin agents, and he has been on three agents, so after three agents the next step is to go to insulin. This stepwise therapy is recommended by many of the major guidelines from the American Diabetes Association and American Association of Clinical Endocrinologists.

MR. BUSKER: We all know how difficult it can be to get some patients to begin insulin therapy. Not necessarily in this case, but beyond the guidelines — the ADA and the AACE and a number of others — is there a specific test that can establish a patient's need for insulin?

DR. GIANCHANDANI: Yes. We can test C peptide.

MR. BUSKER: How does that work?

DR. GIANCHANDANI: The pancreas makes insulin as proinsulin, which is cleaved into a C peptide and insulin in equal amounts. The C peptide has a longer duration, does not go through the liver to get degraded by first pass, and therefore is a very good measurement of the production of insulin in the body or endogenous insulin. We can get a C peptide along with a blood sugar at the same time. Usually we like the blood sugar to be in the 100 mg/dL to 200 mg/dL range, and a C peptide less than 2 ng/mL suggests that the patient has some deterioration in insulin production.

MR. BUSKER: Thank you. Why is this patient's hyperglycemia showing in the morning and hypoglycemia nocturnally?

DR. GIANCHANDANI: Several factors can cause the patient to be hypoglycemic at night and hyperglycemic in the day. First, insulin sensitivity is highest between midnight and 3 am, and that is the same time when the insulin he takes at night has its maximum effect. That causes the patient to have a lower blood sugar at that time.

Additionally, this insulin sometimes may not last long enough and he also may have a dawn phenomenon between 3 am and 6 am that causes his blood sugar to go up. So the night glargine dose drops his blood sugar the most at 3 am, which causes some counter-regulatory hormones to increase blood sugar and these patients become hypoglycemic in the morning.

Also, when his blood sugar drops at night he may take some food to correct it and overcorrect with food for the low blood sugar and his dawn phenomenon may kick in to cause him to be hyperglycemic in the morning but hypoglycemic at night.

MR. BUSKER: Talk to us about strategies to help this patient improve his glycemic control.

DR. GIANCHANDANI: We have a few strategies. We can move the glargine to the morning; sometimes that is helpful to prevent hypoglycemia at night. We can divide the insulin into two doses, giving a dose at night and a dose in the morning, but that increases the number of injections, and most patients do not like to do that. We can have him take a snack at night to prevent hypoglycemia, although this strategy will encourage weight gain and is not ideal. And now we have in our toolbox some newer insulins which are ultralong-acting, and because of their pharmacodynamics and kinetics they cause less hypoglycemia at night and predictable blood sugar in the morning, preventing the hyperglycemia in the morning.

MR. BUSKER: So is this a situation where you'd be likely to recommend an ultralong-acting insulin?

DR. GIANCHANDANI: Yes, very much this would be an area to add an ultralong-acting insulin. They're helpful in patients who get hypoglycemic overnight and hyperglycemic in the morning, which makes it difficult to up-titrate the dose of insulin. Once the patient has switched to an ultralong-acting insulin, these hyper- and hypoglycemic incidents can be reduced significantly.

Additionally, patients also say that quality of life improves with the reduction of hypo- and hyperglycemia and waking up in the night with problems of hypoglycemia and having unpredictable blood sugars in the morning. So yes, this would be a good scenario for patients to start ultralong-acting insulin.

MR. BUSKER: What about titration when switching to an ultralong-acting insulin? What do clinicians need to know?

DR. GIANCHANDANI: Patients can be switched from their current insulins to the ultralong-acting insulins at the same dose.

We could use the 2-0-2 titration, in which the patient or the physician's office titrates the insulin every few days or every few weeks for the patient by checking morning blood sugars and using an average and going up a few units of insulin if they're out of goal and going down a few units if they are hypoglycemic.

MR. BUSKER: Thank you for that case and discussion. We'll return with Dr. Roma Gianchandani in just a moment.

MR. BOB BUSKER
This is Bob Busker, managing editor of *e*Diabetes Review. *e*Diabetes Review is a combination newsletter and podcast program delivered via email to subscribers. Newsletters are published every other month. Each issue reviews the current literature in areas of importance to clinicians treating patients with type 2 diabetes.

In the month following each newsletter, a case-based podcast discussion, like the one you're listening to now, is available to help translate that new clinical information into practice. These podcasts are also available as downloadable transcripts.

Subscription to *e*Diabetes Review is provided without charge or prerequisite.

Continuing education credit for each newsletter and each podcast is provided by the Johns Hopkins University School of Medicine and the Institute for Johns Hopkins Nursing. For more information on this educational activity, to subscribe and receive *e*Diabetes Review without charge, and to access back issues, please go to our website www.ediabetesreview.org

Thank you.

MR. BUSKER: Welcome back to this *e*Diabetes Review podcast. We've been talking with Dr. Roma Gianchandani, Clinical Associate Professor at the University of Michigan in Ann Arbor, about the clinical use of ultralong-acting insulins. Let's continue that clinical perspective with another patient scenario?

DR. GIANCHANDANI: This is a 70-year-old male with type 2 diabetes and mild neuropathy. His A1c is 8% and he has a history of osteoarthritis, GERD, and hypertension. The patient takes sitagliptin and metformin at 50/1000 BID, and glargine U-100 at 48 units at bedtime, which was started four months ago and titrated to the current dose. On home glucose monitoring, his am sugar ranges from 80 mg/dL to 200 mg/dL. Before lunch he runs in the 120 mg/dL to 150 mg/dL range, before dinner 150 mg/dL to 160 mg/dL, and his bedtime sugars are in the 160s, with frequent overnight hypoglycemic episodes. His wife also claims he has night sweats and overnight restlessness two to three times a week as his dose is being titrated. His dose was reduced to 44 units, but he continues blood sugars between 70 mg/dL and 85 mg/dL at night, and on a continuous glucose monitoring trial three to four days a week his am sugars are in the 200 mg/dL range, even if he doesn't have a low sugar at night.

MR. BUSKER: So he has a lot of variability, a lot of hypoglycemia, but not a lot of consistent control. What's the next step in glycemic management for this patient? Would you add another oral agent? Would you discontinue the insulin dose?

DR. GIANCHANDANI: The patient is already on two orals and a large dose of insulin. Another oral would probably not replace this amount of insulin, especially since his A1c is still high with a high insulin dose. So the next step if glargine U-100 lasts for 20 to 24 hours for this patient, the hypoglycemic episodes may continue, and this again would be an excellent opportunity to reduce this hypoglycemia by adding an ultralong-acting insulin.

MR. BUSKER: And is that what you did?

DR. GIANCHANDANI: The patient was switched to degludec and the dose was titrated to 52 units and his morning sugars range between 100 mg/dL and 140 mg/dL. He was in range at meals and his overnight hypoglycemia was reduced remarkably.

MR. BUSKER: So as you anticipated, switching him to ultralong-acting degludec resolved his hypoglycemia and kept his sugars in a far more consistent range. What else do we need to discuss about this patient?

DR. GIANCHANDANI: He developed hematochezia and he had an EGD which was scheduled in the morning, so he had to be NPO after midnight before the procedure. He called to ask how to adjust this new insulin and does he really need this insulin?

MR. BUSKER: That's an interesting concern this case brings up, and one I'd expect will become pretty common. A patient on an ultralong-acting insulin needs to be NPO for a procedure. What's the protocol? Does he need insulin overnight?

DR. GIANCHANDANI: Yes, this is a large dose of insulin, and if he doesn't use it he's going to get very hyperglycemic for the procedure. Some of this insulin, because he is on oral agents, also covers some of his meal insulin, so we have to reduce this dose of insulin. He will still need the insulin but at a lower dose, with an appropriate reduction made for his NPO status.

MR. BUSKER: What dose reduction would you recommend?

DR. GIANCHANDANI: When NPO, he will be hypoglycemic with his full 52 units, as he is using some basal to cover part of his meals. Therefore, 30% to 50% dose reduction is suggested, more toward 50% for a regimen that is basal-heavy, which his is. With degludec, the suggestion is that this reduction be made for two days prior to the procedure because this is such a long-acting insulin, otherwise the patients come in very hypoglycemic at that point. In type 2 diabetes this hypoglycemia is less common than in type 1, so you have to be more careful with your type 1 diabetes patients when you reduce the insulin.

MR. BUSKER: Let me interrupt you just to clarify something. A patient on degludec who has to go for an NPO procedure — the degludec dose reduction needs to be made a full two days prior to the procedure? Is that correct?

DR. GIANCHANDANI: Yes.

MR. BUSKER: Thank you. Now, you were starting to talk about type 1 patients. If this patient happened to be type 1, going for an NPO procedure...

DR. GIANCHANDANI: I would make a similar reduction in a type 1 diabetes patient if they are NPO and make sure that the basal insulin is never held.
It is very important that patients with type 1 diabetes never have their basal insulin held, as they will go into DKA within four to six hours.

MR. BUSKER: And after the NPO procedure, when can the degludec be restarted?

DR. GIANCHANDANI: When the patient starts to eat again, it can be given in full dose. If it is missed for a few hours it is not a problem, because its long-acting nature allows some flexibility of the variable schedule. So, if it's an outpatient procedure when the patient goes back and starts eating, and if it's an inpatient procedure, it all depends on the procedure and what is going to happen to the patient afterward.

MR. BUSKER: We've been talking about ultralong-acting insulin degludec, but in your newsletter you also reviewed the data about another ultralong-acting insulin.

DR. GIANCHANDANI: The other newer ultralong-acting insulin is glargine 300. This can also be used. It is a more concentrated form of glargine and each milliliter has 300 units of glargine instead of 100 units. It does not need to be reduced for two days prior to the procedure (that is not the current recommendation for that insulin, though), but it will have to be reduced the day before the procedure.

MR. BUSKER: Reduction for two days prior to an NPO situation for degludec versus a one-day reduction for glargine 300. What other differences between these two ultralong-acting insulins should clinicians be aware of?

DR. GIANCHANDANI: There are more similarities than differences between the two insulins. They are both ultralong-acting; glargine 300 lasts for about 36 hours, while degludec lasts about 48 hours in the system. They both allow you to flexibly dose the insulin at different times of the day if you forget to take it at the same time. They both have the ability to reduce hypoglycemia overnight and are more predictable.

Some of the head-to-head trials are just emerging, and I talked about one of those trials in the newsletter. There is some data that glargine 300 may cause slightly less hypoglycemia in head-to-head trials and may have slightly less glycemic variability than degludec. But both are good ultralong-acting insulins.

MR. BUSKER: Thank you for that case and discussion. We've got time for one more patient scenario.
DR. GIANCHANDANI: A 70-year-old patient has a history of significant insulin resistance, is in now status poststroke and MI. He is homebound and his meals are delivered by his family. His caregiver comes at variable times of the day. He eats one large meal when his caregiver is in and then grazes throughout the day.

His insulin regimen is 70/30 NPH and regular insulin, which is given only now with his am meal at 28 units. He has hypoglycemia awareness and feels these episodes when he has a small breakfast or if his lunch is delayed. He takes a small box of apple juice at that time. He is hyperglycemic on waking up, in the 200 mg/dL to 300 mg/dL range, and preprandially if he hasn't had insulin at a meal his sugar is also in the 200 mg/dL to 300 mg/dL range.

His exam reveals normal vitals, his weight is 150 kilos. He has some bruising at his injection sites and significant neuropathy with poor pulses.

MR. BUSKER: Poor control, irregular mealtimes, both hypo- and hyper-glycemia. This is a complicated elderly patient who needs help. Let's start with his insulin. That 70/30 mixed insulin he's taking once a day is not giving him full coverage.

DR. GIANCHANDANI: The current mixed insulins last only for about 12 hours. They contain a short-acting insulin and an intermediate-acting insulin, and this patient's combination has NPH and regular. These cover the patients only until dinner if they are taken in the morning. So after dinner all the food he takes in is not covered with insulin, and therefore, he is hyperglycemic in the morning and probably after dinner also.

The fixed combination of 70/30 also may not cover all the meals in the right amount because he may be eating more than that 30% of the insulin that can cover his meals.

MR. BUSKER: Is there a better way to schedule a 70/30 mixed insulin?

DR. GIANCHANDANI: The mixed insulins contain a short-acting component and an intermediate-acting component. If they are taken without a meal, the short acting component causes hypoglycemia, so they should always be taken with breakfast. Additionally, the intermediate acting insulin peaks at a specific time and the patient should have an adequate lunch to prevent this midmorning or midafternoon hypoglycemia. And until a second dose of 70/30 is given at dinner, his morning hyperglycemia cannot be addressed at that point.

MR. BUSKER: It's this qd 70/30 insulin that seems to be the core of this patient's problem. What else can he try? Is there a premixed insulin that can work better with his variable eating schedule?

DR. GIANCHANDANI: Yes, there is a mixed insulin that is FDA approved but is not yet available in the US. It is IDegAspart, which is a combination of degludec, the ultralong-acting insulin we discussed earlier, plus aspart, which is a rapid-acting insulin. The combination can be given at different times of the day. So if the patient eats lunch when the caregiver is there, he can get the dose at that time. The short-acting insulin will cover the meal, and the long- acting degludec will cover all the time until the next day for this patient.

The beauty of this insulin is that if the patient has a large meal at supper one day and lunch the next, this insulin can be given at varied times of the day. Its rapid-acting component covers only the meal and if the patient has two meals and there's a possibility of giving the insulin twice a day, that can also be accommodated. Studies have shown that biphasic insulin given twice a day with IDegAspart actually has lower hypoglycemia than the current biphasic insulin.

A new insulin that has an ultralong-acting and a rapid-acting component should be available shortly. This preparation can be used for this patient and probably will solve some of these problems.

MR. BUSKER: What if this was a type 1 patient? Would the IDeg-Aspart still be appropriate?

DR. GIANCHANDANI: Yes, the IDegAspart can also be given for this patient. It would be one injection with a meal for the patient, but in a type 1 patient the other meals would have to be covered by a rapid-acting insulin given separately from the IDegAspart when the patient eats. Additionally, if you have a type 1 patient who you are not concerned with tight glucose control, you could also use the IDegAspart twice a day, and that would cover a couple of meals and also save one injection for the patient.

The advantage in a type 1 diabetes patient would be that you're reducing the injections. If the patient eats fewer than three meals a day it will be a very convenient insulin for the patient to use.

MR. BUSKER: In your newsletter issue, you reviewed data about an ultrarapid-acting insulin. Is that product available in the US?

DR. GIANCHANDANI: Yes, the ultrarapid-acting insulin aspart is available. It is aspart insulin with added vitamin B3 or niacinamide and L-arginine. Niacinamide increases the absorption of the insulin, allowing much faster entry into the bloodstream, and L-arginine increases the stability. It is helpful for patients who have postprandial hyperglycemic excursion and can be given as soon as the patient starts eating and up to 20 minutes after the patient starts eating, so it provides some flexibility in dosing the meal insulin.

MR. BUSKER: Thank you for bringing us today's cases and discussion. Let's wrap things up now by reviewing the key points of what we've talked about today in light of our learning objectives. To begin: situations in which patients can benefit from ultralong-acting insulins.

DR. GIANCHANDANI: Patients who benefit from ultralong-acting insulins have significant hypoglycemia overnight and are still hyperglycemic in the morning would benefit from these insulins. In patients you do not want to have any hypoglycemia, like patients who have cardiovascular disease or hypoglycemia awareness, the ultralong-acting insulins are also helpful. Patients, of course, want the best insulin and these insulins are more physiologic and predictable, so they would be another group of patients who you would consider for these types of insulin.

Patients who are very insulin-resistant and need large amounts of insulin would be another group. Both the ultralong-acting insulins come in more concentrated form. The glargine is U-300, so each unit of insulin has 300 units; and the degludec comes in a U-200 preparation, which is also more concentrated, so these volumes of insulin would be much lower and therefore would prevent the lipodystrophy in the group of patients. These are some of the scenarios in which patients would benefit from ultralong-acting insulin.

MR. BUSKER: And our other learning objective: the potential negatives of these ultralong-acting insulins.

DR. GIANCHANDANI: Because of the ultralong-acting nature of these insulins, if a patient stops eating, such as in preparation for surgery, or if they have any renal dysfunction, these ultralong-acting insulins cause prolonged hypoglycemia which has to be dealt with at that point. Additionally, these insulins are very expensive and the coverage by insurance is somewhat difficult at the moment.

MR. BUSKER: Dr. Roma Gianchandani from the University of Michigan in Ann Arbor, thank you for participating in this *e*Diabetes Review Podcast.

DR. GIANCHANDANI: Thank you so much for inviting me, I enjoyed this discussion immensely.

MR. BUSKER: To receive CME credit for this activity, please take the post-test at www.ediabetesreview.org
This podcast is presented in conjunction with the *e*Diabetes Review newsletter, a peer-reviewed literature review certified for CME/CE credit, emailed monthly to clinicians treating patients with type 2 diabetes.

This activity has been planned and implemented in accordance with the accreditation requirements and policies of the Accreditation Council for Continuing Medical Education (ACCME) through the joint providership of the Johns Hopkins University School of Medicine and the Institute for Johns Hopkins Nursing. The Johns Hopkins University School of Medicine is accredited by the ACCME to provide continuing medical education for physicians.

The Johns Hopkins University School of Medicine designates this enduring material for a maximum of 0.5 *AMA PRA Category 1 credit*™. Physicians should claim only the credit commensurate with the extent of their participation in this activity.
The Institute for Johns Hopkins Nursing is accredited as a provider of continuing nursing education by the American Nurses Credentialing Center's Commission on Accreditation.

For nurses, this 0.5 contact hour Educational Activity is provided by the Institute for Johns Hopkins Nursing. Each podcast carries a maximum of 0.5 contact hour.

This educational resource is provided without charge, but registration is required. To register to receive *e*Diabetes Review via email, please go to our website: www.ediabetesreview.org**.**

The opinions and recommendations expressed by faculty and other experts whose input is included in this program are their own. This enduring material is produced for educational purposes only.

Use of the names of the Johns Hopkins University School of Medicine and the Institute for Johns Hopkins Nursing implies review of educational format, design, and approach. Please review the complete prescribing information for specific drugs, combinations of drugs, or use of medical equipment, including indication, contraindications, warnings, and adverse effects, before administering therapy to patients.

***e*Diabetes Review is supported by educational grants from Merck & Co., Inc., NovoNordisk, and Sanofi.**

CME/CE INFORMATION

ACCREDITATION STATEMENT
This activity has been planned and implemented in accordance with the accreditation requirements and policies of the Accreditation Council for Continuing Medical Education (ACCME) through the joint providership of the Johns Hopkins University School of Medicine and the Institute for Johns Hopkins Nursing. The Johns Hopkins University School of Medicine is accredited by the ACCME to provide continuing medical education for physicians.

CREDIT DESIGNATION STATEMENT
Physcians:
The Johns Hopkins University School of Medicine designates this enduring material for a maximum of 0.5 A*MA PRA Category 1 credit*™. Physicians should claim only the credit commensurate with the extent of their participation in this activity.

Nurses:
For nurses, this 0.5 contact hour Educational Activity is provided by the Institute for Johns Hopkins Nursing. Each podcast carries a maximum of 0.5 contact hour.

POLICY ON SPEAKER AND PROVIDER DISCLOSURE
It is the policy of the Johns Hopkins University School of Medicine and the Institute for Johns Hopkins Nursing that the speaker and provider globally disclose conflicts of interest. The Johns Hopkins University School of Medicine OCME has established policies that will identify and resolve conflicts of interest prior to this educational activity. Detailed disclosure will be made prior to presentation of the education.

INTERNET CME/CE POLICY

DISCLAIMER STATEMENT

STATEMENT OF RESPONSIBILITY

STATEMENT OF NEED

INTENDED AUDIENCE

CONFIDENTIALITY DISCLAIMER FOR CME ACTIVITY PARTICIPANTS

HARDWARE & SOFTWARE REQUIREMENTS

COMPLETE CME INFORMATION

This activity was developed in collaboration with DKBmed.