Embracing the Insulin Revolution in the Ambulatory Care Setting

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IN BRIEF Recent additions of various new formulations of insulin to the U.S. marketplace have increased the number of treatment options available to people living with diabetes. However, it is important to take into consideration the implications of these new insulins in terms of patient safety and medication errors, integration with electronic medical records, and financial considerations. This review outlines several considerations for practitioners regarding the implications of these new insulin products for ambulatory care practice.

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Health care professionals working in the area of diabetes management have likely noticed what many consider to be an explosion in the number and variety of insulin products added to the market in recent years. Another article in this *Diabetes Spectrum* From Research to Practice section (p. 136) provides an overview of the different types of available insulins and the multiple variations in their characteristics. It is important to note that, despite the many positive changes these insulins bring to people living with diabetes, there is still the potential for downstream negative consequences. These can include issues related to electronic medical records (EMRs), medication errors that can result in patient harm, and cost considerations that must be fully understood and acknowledged. Although this is not an exhaustive list of the necessary considerations, this

article presents a good starting place for practitioners to more fully grasp what these insulins can contribute to modern practice and patient care.

Patient Safety and Medication Errors

One of the most important factors to consider when any medication enters the market is patient safety and the potential for medication errors. The introduction of new insulins and new concentrations of existing insulins is certainly no exception. It is important to note that the recent use of pen devices for delivery of these new insulin formulations is an important step in that it minimizes the potential for dosing errors that can occur when patients draw up doses out of a vial using a syringe, as has been seen with U-500 regular insulin, the first available concentrated insulin product (1,2).

Administering the Correct Insulin at the Correct Time

As will always be the case for people who use both basal and bolus insulin, it is important to administer the correct type of insulin, in the correct dose, and at the correct time. Various approaches have been used to help patients differentiate among the various insulin products they may use. For example, concentrated insulin glargine comes in a pen featuring green shading and the phrase "300 units/mL (U-300)" marked in a yellow box immediately beneath the name of the medication (3). This is an important counseling point about this medication to help patients readily distinguish it from their other medications, especially their bolus insulin.

Similarly, insulin degludec is available in two separate concentrations (U-200 and U-100), with the only significant difference in appearance between the two concentrations being a darker forest green label for the U-200 formulation and a brighter spring green label for the U-100 formulation (4). Of note, in Europe, the differences in appearance between these two products are much more apparent, with the U-200 formulation having "200" marked in a bright red box immediately beneath the name of the medication and a green and white hash-mark design on the pen labeling, as opposed to the solid green labeling of its U-100 counterpart (5). One additional safety matter for patients to know is that the U-200 insulin degludec pen can only be dosed in 2-unit increments, whereas the U-100 degludec is dosed in 1-unit increments (4).

The insulin lispro U-200 pen takes a similar approach to the European version of insulin degludec by adding the phrase "200 units/mL (U-200)" in purple text within a white box just below the name of the medication (6). Additionally, the background color of the label is purple with a partial checkerboard design rather than the all-white background of the U-100 insulin lispro pen device (6). Patients should be well educated on the key distinguishing characteristics to look for on each of their insulin pens before administering a dose in order to be more successful at using the correct insulin at the correct time of day.

Ordering the Correct Insulin When Writing Prescriptions

The introduction of new insulins and new concentrations of existing insulins presents a new challenge when writing prescriptions for patients to fill at their local pharmacy. Manufacturers took several different approaches when introducing their new medications to the market. In one approach, Sanofi branded its concentrated version of insulin glargine under an entirely new brand name, Toujeo. Although the generic names are the same, physicians and other prescribers can identify the version of insulin glargine that they are wanting to prescribe by using the particular brand name of the desired product.

As an alternative, some manufacturers maintained the same brand names for all of the different concentrations of insulins (e.g., Eli Lilly and Company's Humalog and Novo Nordisk's Tresiba) and added the designation "U-100" or "U-200" to the name and label. In this situation, it is especially important to ensure that the desired concentration is prominently written or otherwise noted on the prescription. This would include being especially attentive when selecting these insulins from a search box within an EMR since these insulins are likely to be listed in close proximity to each other.

Drawing Up Insulin Out of a Pen Using a Syringe

It may sound unnatural to treat an insulin pen like a vial and draw doses up using a syringe, but this certainly does happen. Often, this is the result of a cost issue; uninsured patients' out-of-pocket costs for insulin syringes are much less than for pen needles, and the syringes often are easily accessible through charity programs facilitated by clinics, health systems, and other entities.

However, the package inserts for each of the insulin pens explicitly state that patients should not draw up insulin out of the pens using a syringe (3,6,7). Doing so can result in multiple problems, including damage to the pen that may prevent correct administration of future doses, introduction of air into the insulin pens that can result in underdosing of subsequent doses, and, most importantly, administration of an accidental overdose of a concentrated insulin when using a U-100 syringe. For insulin lispro U-200 specifically, there is an added safety mechanism with the addition of a yellow label prominently placed on the clear cartridge holder of the insulin pen bearing the statement "DO NOT TRANSFER TO A SYRINGE; SEVERE OVERDOSE CAN RESULT" and a triangle with an exclamation point in the middle (6). Regardless of which insulin is prescribed, patients must be explicitly counseled about the importance of not drawing up insulin from a pen using a syringe to maximize patient

safety and minimize future administration errors.

EMR Barriers

Whenever a new product receives approval from the U.S. Food and Drug Administration (FDA) and enters the market, there is always a period of time during which the health care system needs to find ways to adapt current processes and procedures, especially in today's age of EMR systems. Most notably, many EMR systems have a central database of all of the different medications, dosage strengths, and formulations that is made available to individual health systems, clinics, and other end-users; providers choose appropriate medications and dosages from this list. This system is designed to minimize medication errors and increase efficiency by limiting the amount of free text a user must type to make a selection. When a user enters the individual components of a prescription (e.g., dose, route, and frequency) into boxes of discrete data, the EMR system is able to cross-reference that information with internal algorithms containing generally accepted standards to enhance medication safety (e.g., it can identify whether a given dose is too high for a patient's renal function or the noted frequency is not recommended). Health systems and other entities can also further restrict the medications available to end-users from within this database to influence providers' prescribing practices and assist with formulary management, especially in the inpatient setting.

However, a lag period exists between the time a new medication enters the market and the time when the specifics of using the medication are entered into EMR formularies; at present, the length of this lag time has not been clearly identified in the literature. Consequently, during this lag time, the lack of a prespecified medication order to select in the EMR results in practitioners using free text boxes to order new medications. Although the use of free text when ordering prescriptions can increase the risk of medication errors (8), this risk is dramatically increased in the case of medications that are new to the market and for which there may be general unawareness of the specific details for each new product on the part of health care team members. This unawareness includes everything from minor elements (e.g., how many units of insulin are in each pen and how many pens are in each box) to more major concerns (e.g., the necessary and appropriate details that should be included on the prescription for insulins with different concentrations that share a common brand name). Table 1 was developed to assist prescribers in ensuring that correct information is included on each prescription by providing all of the information for each of the insulins in one location (3,6,7,9–14).

Aside from the patient safety concerns discussed earlier, there are several logistical barriers that can arise and delay patient care if any elements of the prescription are incorrect (e.g., prescribing a partial box or an incorrect number of pens). To avoid this, it is imperative for EMR systems to upload and incorporate product-specific information for new products as soon as possible and for individual health systems to ensure that all end-users have access to these selections within the EMR medication database (especially for institutions that restrict prescriber access to the database).

Financial Barriers to Newer Insulins

Anytime a new medication enters the market, cost and insurance coverages always are key elements of the discussion. Innovations in medicine and technology are not fully realized unless they are accessible to the people who need them most. In keeping with this tradition, cost is certainly a critical consideration for the new insulin formulations. First and foremost, it is important to consider the likelihood of a person actually benefiting from a newer insulin analog, since some patients may not need to switch to a newer, more expensive agent (e.g., less tight glycemic control is warranted, the patient is already well managed on the current regimen, or the patient has a relatively low total daily dose of insulin).

Although insurance coverage varies from state to state and from patient to patient, the availability of manufacturers' patient assistance programs is generally a constant factor across the country; therefore, these details are reviewed below. Of note, many manufacturers have introduced copayment assistance cards to decrease the out-of-pocket costs for patients with insurance if their specific insurance plan does not cover the specific medication. Although these can be helpful for patients, it is important to remember that many of these programs come with restrictions that include a limited timeframe for use (e.g., a maximum of 12 months), after which an alternative treatment regimen may need to be considered if the medication has not been added to the specific plan's formulary by that time.

Concentrated Insulin Glargine (U-300)

The Sanofi Patient Connection program provides information about how eligible patients can apply to receive concentrated insulin glargine through the manufacturer's patient assistance program (15). Patients must not have prescription coverage or access to the prescribed product or treatment via their insurance. Additionally, patients must not be eligible for state or federal insurance programs (although some exceptions exist for certain Medicare Part D beneficiaries) and must have a household income <250% of the federal poverty level. For patients with commercial insurance (excluding commercial Medicare plans), there is a copayment assistance card that can reduce patients' copayment by as much as $400, down to a copayment of no more than $15 (16). Of note, this copayment assistance is

only available for a maximum of 12 months of treatment, and patients will have to pay the full copayment for the prescription thereafter.

Insulin Degludec (U-100 and U-200)

Novo Nordisk also offers a copayment assistance card for patients with commercial insurance plans (excluding commercial Medicare plans) that have high copayments for insulin degludec (17). With this card, patients can receive a maximum savings of $500 per prescription, bringing their copayment down to no more than $15. At the time of writing, insulin degludec was not available through Novo Nordisk's patient assistance program for uninsured patients.

Concentrated Insulin Lispro (U-200)

The Lilly Cares program provides information on Eli Lilly and Company's patient assistance program (18). Patients must not have prescription coverage or be eligible for state or federal insurance programs (although some exceptions exist for certain Medicare Part D beneficiaries) and must have a household income <300% of the federal poverty level. For patients with commercial insurance plans (excluding commercial Medicare plans), there is a copayment assistance card that can reduce patients' copayment by as much as $100 per month, down to a copayment of as little as $25 per prescription (19). Of note, this copayment assistance is only available for the first 24 fills of concentrated insulin lispro (or until program expiration, which at the time of writing was scheduled for 31 December 2018), and patients will have to pay their full copayment for the prescription thereafter.

Importance of Two-Way Communication Between Patients and Providers

Medication costs are extremely important to consider when developing patient treatment plans. Even if patients currently have adequate

TABLE 1. Product-Specific Characteristics of FDA-Approved Insulin Analog Pens (3,6,7,9–14)

Brand Name	Generic Name	Concentration (units/mL)	Units/Pen	mL/Pen	Pens/Box	mL/Box	Maximum Dose for Pen to Dial (units)	Important Notes
Basal Insulin Analogs								
Toujeo Solostar	Insulin glargine	300	450	1.5	3 or 5	4.5 or 7.5	80	
Lantus Solostar	Insulin glargine	100	300	3	5	15	80	
Basaglar KwikPen	Insulin glargine	100	300	3	5	15	60	
Tresiba FlexTouch	Insulin degludec	100	300	3	5	15	80	
		200	600	3	3	9	160	Actual dose must be an even number (only dials in increments of 2)
Levemir FlexTouch	Insulin detemir	100	300	3	5	15	80	
Bolus Insulin Analogs								
Humalog KwikPen	Insulin lispro	100	300	3	5	15	60	
		200	600	3	2	6	60	
Novolog FlexPen and FlexTouch	Insulin aspart	100	300	3	5	15	80	
Apidra Solostar	Insulin glulisine	100	300	3	5	15	80	
Combination Products								
Ryzodeg 70/30 FlexTouch	Insulin degludec/ insulin aspart	100	300	3	5	15	80	Each administered dose contains 70% insulin degludec and 30% insulin aspart

insurance coverage, formularies and insurance providers may change, necessitating changes in their diabetes treatment plan. Similarly, many patients with Medicare Part D coverage experience a significant amount of stress toward the end of each year when they fall into the Medicare coverage gap (commonly referred to as the "donut hole").

One of the best approaches in this situation is to avoid the gap (if possible), which can be done by reviewing the individual patient's coverage at the beginning of the year (including total medication costs and total out-of-pocket costs). Formularies can change from one year to the next, and it is important for patients to stay up to date with these changes to avoid interruptions in their treatment. If a patient does fall into the coverage gap, some manufacturers offer copayment assistance for certain Medicare Part D beneficiaries, although the fate of these programs is uncertain given current plans to close the Medicare coverage gap by 2020. Another alternative would be to consider switching patients to a different insulin regimen that has lower out-of-pocket costs (e.g., NPH insulin, regular insulin, or a premixed 70/30 insulin product).

In each of these scenarios, it is important to maintain open lines of communication with patients to avoid interruptions in treatment. Patients should be informed that enrollment in assistance programs and other treatment alterations may take weeks to complete, and advanced notice will be required to ensure a successful outcome and minimize interruptions to treatment. It would also be beneficial to check in with patients who are enrolled in Medicare Part D programs partway through each year to evaluate the total amount they have spent on medications and assess their risk of falling into the Medicare coverage gap.

Finally, it is important to educate patients about the importance of not using old medicines they may have around the house, especially when considering possible measures to reduce their costs. Insulin is an extremely sensitive medication, and proper storage and handling are required to ensure its safe and effective use.

Dose Conversions Between Insulin Analogs

Every patient responds to insulin differently, so transitions between insulins can present a challenge with regard to avoiding both hyper- and hypoglycemia. This is especially true for the newer insulin analogs (i.e., glargine U-300 and degludec) given their extended durations of action and their extended time to reach a steady state.

To date, the majority of information about dosing conversions during transitions between insulin products comes from controlled clinical trials rather than from actual clinical practice. Additionally, the available literature mainly provides recommendations about how to switch patients to the new agents, with almost no information available about switching patients from these regimens, which can also be a difficult transition. When transitioning between any basal insulin regimens, it is especially important for patients to increase the frequency of their self-monitoring of blood glucose to identify and mitigate the risks of hypo- and hyperglycemia.

Concentrated Insulin Glargine (U-300)

When changing from another once-daily basal insulin to concentrated insulin glargine, consider starting concentrated insulin glargine at the same dose (3). Based on clinical trials, patients may require a higher daily dose of concentrated insulin glargine to maintain the same level of glycemic control they had on their previous basal insulin regimen (3). When changing from twice-daily NPH insulin, the recommended starting dose of concentrated insulin glargine is 80% of the total daily NPH insulin dose (3). Conversely, for patients interested in switching from concentrated insulin glargine to NPH insulin, consider switching to the same daily dose (either once daily or divided into twice-daily injections) with the understanding that a dosage increase may be necessary because of differences in the two products' pharmacokinetics.

Insulin Degludec (U-100 and U-200)

Insulin degludec is the newest basal insulin to enter the U.S. market, so clinical experience with this medication in the United States is even more sparse than with other products. However, degludec has been on the market in Europe and other areas around the world since 2013 (5). Recommendations from the package insert suggest using the same total daily dose the patient was previously on when converting from another long- or intermediate-acting insulin to insulin degludec (7). For people with type 1 diabetes and an A1C <8% or those switching from twice-daily basal insulin regardless of their diabetes type, consider a dose reduction of 20% when switching to insulin degludec (20).

Concentrated Insulin Lispro (U-200)

The new concentrated insulin lispro does not require any dose adjustments when switching from a regimen of multiple daily injections of regular insulin lispro or other rapid-acting insulin analogs. The main benefit of this new concentrated formulation is that patients can switch pens less frequently, with the new pens holding 600 units in each rather than the traditional 300 units (6). This is especially important for patients on higher doses who use multiple pens in a week or even in a month.

Conclusion

The new insulins recently approved by the FDA bring tremendous potential for benefit to many people living with diabetes by introducing a broader variety in treatment options to improve glycemic control. However, providing

excellent care and improving patient safety require both health care professionals and patients to be well versed in the different available formulations and the nuances of differences among them. Additionally, it is imperative to work with the informational technology staff at one's health system and the company providing the EMR system to ensure that these new products are appropriately loaded into the computerized prescribing system to minimize guesswork by prescribers and dispensing pharmacies and decrease the likelihood of incorrect and incomplete entries. Finally, assessing patients' delivery device technique and working with patients individually to identify treatment goals, expectations, and cost considerations are crucial for ensuring that the optimal treatment is selected.

Duality of Interest

No potential conflicts of interest relevant to this article were reported.

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