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**JAMA viewpoint offers practical tips for human insulin for type 2 diabetes -  
June 20, 2017**

**Executive Highlights**

- Drs. Kasia Lipska, Irl Hirsch, and Matthew Riddle recently published a viewpoint in JAMA advocating for human insulin as a type 2 diabetes treatment. The authors emphasize its low cost and suggest that the advantages of insulin analogs over human insulin are less clear in type 2 diabetes vs. type 1.
- On the other hand, human insulin is a less flexible product that increases hypoglycemia risk. We're wary that opinions like this ask patients to settle for suboptimal diabetes care, instead of looking for solutions elsewhere in the healthcare system to make insulin affordable. In our view, greater pricing transparency from PBMs is a good place to start.

A recent [JAMA viewpoint](#) by Drs. Kasia Lipska, Irl Hirsch, and Matthew Riddle advocates for the use of human insulin in type 2 diabetes due to its low cost, arguing that the advantages of insulin analogs over human insulin are less clear in type 2 diabetes vs. type 1. The article rightfully identifies cost as a key consideration in diabetes care, given the vast size of this epidemic and the many patients on high-deductible health insurance plans (HDHPs) who shoulder much of the expense for every prescription. A table embedded in the paper (see below) reflects non-trivial price differences between human and more advanced insulin products, including Sanofi's Lantus and Toujeo, Novo Nordisk's Levemir and Tresiba, and Lilly/BI's Basaglar on the basal side, plus Sanofi's Apidra, Novo Nordisk's NovoRapid, and Lilly's Humalog on the prandial side. The article aims to provide a practical guide to human insulin therapy - while we certainly agree that it's imperative that physicians and other healthcare providers know how to treat with insulin for patients with no other options, we hope that human insulin remains a "last resort," rather than the return to a preferred status as treatment for type 2 diabetes.

In describing how to treat with human insulin, the article actually highlights a number of its limitations. In sharp contrast to next-generation basals (Tresiba and Toujeo), which come with a very flat PK/PD profile and long duration of action, human N insulin does not reliably cover 24 hours and necessitates a more complex dosing regimen of more than one injection per day. Human N insulin is thus a more error-prone product, and we all know insulin dosing and titration are already challenging enough. Similar pitfalls are reflected in the rapid-acting field as well. Unlike rapid-acting insulin analogs that start working within ~15 minutes, the time to onset for human R insulin is  $\geq 30$  minutes. Both basal and bolus human insulin are thus less flexible products (a mealtime dose of human insulin has to be much more thoughtfully-timed, increasing patient burden). Moreover, both confer a substantially higher hypoglycemia risk vs. insulin analogues. Hypoglycemia is an incredibly important outcome beyond A1c that contributes major costs to the healthcare system in the form of hospitalizations, emergency care, productivity loss, and more - we urge payers and providers to think about this and other long-term consequences of suboptimal diabetes care before pushing forward with human insulin as the cost-saving solution for type 2 diabetes. Hypoglycemia is thought to be less common in type 2 diabetes (due to greater residual beta cell function and increased insulin resistance). That said, [multiple studies](#) have still shown a substantial hypoglycemia benefit for Tresiba over even first-generation basal analog Lantus in patients with type 2 diabetes - while the direct comparison of Tresiba to human insulin has not been done, we can only assume that the benefit would be even more pronounced. While we acknowledge that human insulin may be the only feasible option for some in the short term, in the long term we'd prefer to see improved reimbursement prospects for superior insulin therapy and pricing transparency at all stages of the system, including PBMs. Dr. Hirsch has [previously lamented](#) that new physicians do not learn how to titrate human insulin and we're glad that he is taking steps to address this

knowledge gap at hand (this follows a [brand-new talk](#) on this topic at his annual Endo Fellows meeting). At the same time, we do not view widespread use of human insulin as the solution to the current insulin pricing controversy and we would hope that opinions like this one published in JAMA would be thoughtful in conveying this nuance. We certainly would not want payers to read viewpoints like these and force patients with type 2 diabetes to switch to human insulin en masse and we hope that such educational efforts from leading physicians can be accompanied by calls to all players in healthcare to collaborate on making insulin affordable.

- **Dr. Hirsch has certainly become well-known for his strong commentary on the insulin pricing front:** Read about his [third annual rant](#) in *Diabetes Technology and Therapeutics*, his [editorial](#) titled "Insulin in America," and the opinions he shared at [CMHC 2016](#). We're not surprised to see him as an author on a cost-related diabetes paper, but we also want to highlight his previous calls-to-action for greater insulin pricing transparency from manufacturers as well as PBMs, as we continue to believe that is the best course of action to optimize patient care.

	Time of Action			Use	Trade Name	Price, \$ <sup>a</sup>	
	Onset	Peak	Duration			per Vial	per Carton
Synthetic human insulin							
NPH (N)	2-4 h	4-10 h	12-18 h	Once at bedtime or twice daily	Novolin N Humulin N	25 100	NA 288
Regular (R)	30-60 min	2-3 h	8-10 h	0-30 min before meals	Novolin R Humulin R	25 100	NA NA
Premixed 70/30 N/R	30-60 min	2-6 h	12-18 h	Before breakfast and dinner	Novolin 70/30 Humulin 70/30	25 100	NA 288
Insulin analogues							
Degludec	1 h	No peak	>40 h	Once daily	Tresiba	NA	390-452
Detemir	3-4 h	3-9 h	6-24 h	Once or twice daily	Levemir	221-284	330-409
Glargine	2-6 h	No peak	20-24 h	Once or twice daily	Lantus Toujeo Basaglar	178 NA NA	266 275-347 <sup>b</sup> 332
Aspart	5-15 min	30-90 min	4-6 h	0-15 min before meals	Novolog	210-290	403-538
Glulisine	5-15 min	30-90 min	4-6 h	0-15 min before meals	Apidra	185	400
Lispro	5-15 min	30-90 min	4-6 h	0-15 min before meals	Humalog	174	322
Premixed	5-15 min	2-4 h	14-24 h	0-15 min before breakfast and dinner	Novolog 70/30 Humalog 75/25 Humalog 50/50	218-300 179 179	403-538 322 322
Abbreviations: NA, not applicable; NPH, neutral protamine Hagedorn.				for some drugs. One vial contains 10 mL of insulin (1000 U). One carton contains five 3-mL pens of insulin (1500 U).			
<sup>a</sup> Approximate prices are based on goodrx.com, which searches for the lowest local pharmacy prices (accessed June 7, 2017). Insurance co-pays are typically less. Prices may vary based on eligibility requirements so ranges are presented				<sup>b</sup> Three 1.5-mL pens of 300 U per mL (1350 U).			

-- by Payal Marathe, Helen Gao, and Kelly Close