

Optimizing the Use of NPH Insulin in Patients with Type 2 Diabetes Mellitus

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The Centers for Disease Control 2020 National Diabetes Report estimates individuals with diabetes represent 10.5% of the United States (US) population.¹ Improving glycemic control in these patients has a substantial impact on reducing co-morbidities and improving resource utilization. Appropriate product selection, with consideration of patient's payment mechanism, can be a crucial step in meeting therapy goals. The increasing burden of insulin costs is challenging for patients with limited resources. Insulin prices continue to rise, with a 262% increase in list prices and 51% jump in net prices (includes concessions/rebates made by the manufacturer when reporting sales) over the last two decades.² The incidence of cost-related medication non-adherence has been reported to be as high as 16.5% in adults with diabetes and 1.24 times more common in patients taking insulin compared to those not taking insulin.³ NPH insulin, which is less costly than long-acting insulin analogs, is a valuable, underutilized therapeutic option. However, the long-acting insulin analogs, which are frequently perceived as superior products, are more commonly prescribed. This newsletter will discuss characteristics of NPH insulin products and strategies for providers to utilize when switching patients to NPH if appropriate.

NPH vs. Long-Acting Insulin Analogs

Either NPH insulin or a basal insulin analogs are an appropriate option for patients with type 2 diabetes mellitus (T2DM) requiring additional glucose lowering beyond oral therapies. Hemoglobin A1c (HbA1c) reductions between NPH insulin and basal insulin analogs are similar.⁴ Clinical trial data suggests a modest benefit in reduced risk of nocturnal hypoglycemia with long-acting insulin analogs (glargine, detemir and degludec) compared to NPH insulin.⁴ However, the incidence of severe hypoglycemia with long-acting insulin analogs and NPH in patients with T2DM is similar.⁵ This was substantiated by a recent observational, retrospective review which analyzed the comparative hypoglycemia rates of long-acting insulin analogs (glargine or detemir) to NPH insulin.⁵ Long-acting insulin analogs were associated with a 1.5% incidence of hypoglycemia-related emergency department visits or hospitalizations compared to 2.0% incidence with NPH insulin, the difference was not determined to be statistically or clinically different.⁵ There is a lack of evidence to support clinically relevant differences for most outcomes when comparing long-acting insulin analogs to NPH. Additional comparative evidence between NPH and concentrated insulins (insulin glargine U-300) and ultra-long acting insulin (insulin degludec) is needed.⁴

NPH Insulin

If NPH is the most appropriate insulin option for a patient, there should be careful consideration related to initiating or switching therapy. The recommendation for initiating NPH insulin is 0.1 – 0.2 units per kilogram, which is most commonly started as a once daily dose at bedtime or twice daily.⁶ Blood glucose monitoring should always accompany any insulin initiation or change. For most basal insulins, one fasting measurement daily is usually sufficient. NPH can be mixed with short or rapid acting insulin, reducing injections for patients.

Switching Between Insulin Products

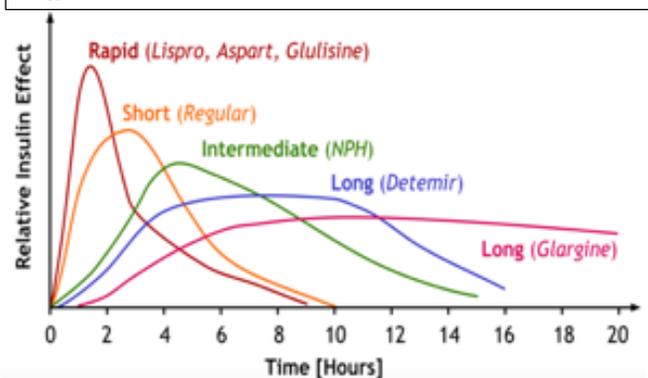
Consideration of insulin properties is an important step in the process of switching insulin. The duration of insulin action is important when changing a patient's regimen. **Table 1** and **Figure 1** provide insulin characteristics and dosing recommendations.

Table 1. Characteristics of Basal Insulin⁶

Basal Insulin	Duration of Action	Dosing Interval
NPH Insulins		
NOVOLIN N	Up to 24 hours	Once or twice daily
HUMULIN N	Up to 24 hours	Once or twice daily
Basal Insulin Analogs		
Insulin glargine (BASAGLAR, LANTUS)	Median 24 hours	Once daily
Insulin glargine U300 (TOUJEO)*	> 24 hours	Once daily
Insulin detemir (LEVEMIR)	7.6 – 24 hours (dose-dependent)	Once or twice daily
Insulin degludec (TRESIBA)	At least 42 hours	Once daily at any time

* Concentrated glargine formulation for patients requiring at least 20 units per day. May take up to 5 days to see maximal effect.

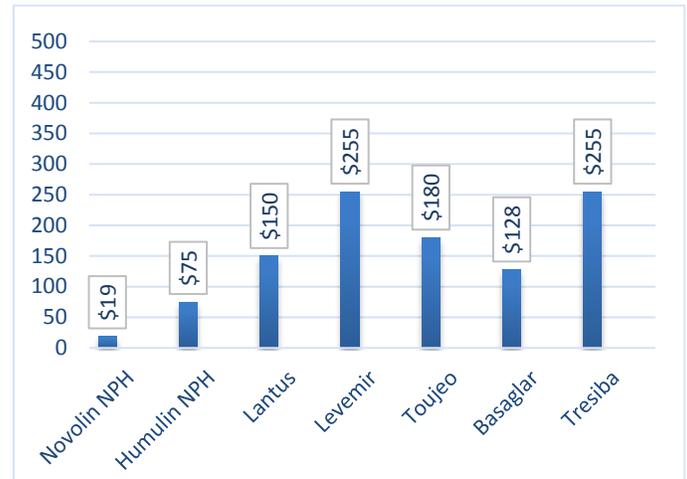
Figure 1. Duration of Action of Insulin Products⁷



There are many reasons for switching between insulin products, such as adverse reactions (e.g., hypoglycemia), cost, and insulin volume to be injected. If patients are switching between human insulin brands, such as Humulin N to Novolin N, the amount injected daily can be kept the same. If the patient has a history of hypoglycemia or no specific recommendations are available to facilitate switching insulins, reduction in insulin dose by 20% is a conservative approach to minimize adverse reactions. Specific recommendations for switching from basal insulins to NPH are provided in **Table 2**. Switching from NPH insulin to a different basal insulin is recommended for some patients because of clinical need, ease of use or cost-related factors (such as formulary or insurance preference). For this reason, guidance for switching from insulin NPH to a basal insulin analog is also presented in **Table 2**.

insulins; therefore, selection of the most cost-effective option should be individualized dependent on patient's insurance coverage. Costs of insulin products based on retail prices are displayed below in Figure 2.

Figure 2. RETAIL Basal Insulin Costs



* Prices based on cost for 25 units/day for 30 days (price for vials unless only available in pen formulation) from GoodRx.com. Accessed May 21, 2020.

- For OHP Fee-For-Service **Lantus** is currently the most cost-effective basal insulin option followed by **Levemir**
- For cash paying patients **NPH insulin** provides the most value

Table 2. Switching to or from NPH Insulin⁸

Product Switch	Conversion
Insulin detemir (LEVEMIR) to NPH	<ul style="list-style-type: none"> Convert unit-per-unit* Give NPH twice daily
Insulin glargine U100 (LANTUS, BASAGLAR) or insulin glargine U300 (TOUJEO) to NPH	<ul style="list-style-type: none"> Divide NPH dose equally or 2/3 in the AM and 1/3 before dinner or at bedtime No specifics available for TOUJEO conversion. Consider 20% dose reduction
Insulin degludec (TRESIBA) to NPH	<ul style="list-style-type: none"> Limited information to guide switch Consider unit-per-unit conversion Give NPH twice daily Divide NPH dose equally or 2/3 in the AM and 1/3 before dinner or at bedtime
NPH insulin to insulin glargine U100 (LANTUS, BASAGLAR) or insulin glargine U300 (TOUJEO)	<ul style="list-style-type: none"> NPH given once daily can be switched unit-per-unit NPH given twice daily should have total daily dose reduced by 20% and initiate new insulin as a once daily injection
NPH insulin to insulin detemir (LEVEMIR)	<ul style="list-style-type: none"> Convert unit-per-unit May need additional insulin detemir Insulin detemir can be give once daily or divided twice daily
NPH insulin to insulin degludec (TRESIBA)	<ul style="list-style-type: none"> Convert unit-per-unit and give once daily*

* Dose reduction of 20% in total daily dose is also recommended

Conclusion

Insulin selection should be determined by patient specific characteristics. In the absence of a compelling need for a specific long-acting insulin product, value should be taken into account to reduce the economic burden for patients at risk for non-adherence due to resource constraints. There is no one basal insulin product that can be universally recommended for all patients. It is important to be mindful of the basal insulin that is the most clinically appropriate and represents the most cost-effective option.

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Comparative Basal Insulin Costs

NPH insulin can be a low-cost option for uninsured patients and those that cycle on and off Oregon Health Plan (OHP) coverage. NPH may also represent an affordable insulin for patients with high deductible insurance plans, those on Medicare and when NPH is on a lower tier copay than branded products. **Insurance plans may receive discounts on**

References:

1. Centers for Disease Control. National Diabetes Statistics Report 2020. Available at: <https://www.cdc.gov/diabetes/pdfs/data/statistics/national-diabetes-statistics-report.pdf>. Accessed April 20, 2020.
2. Hernandez I, San-Juan-Rodriguez A, Good CB, Gellad WF. Changes in List Prices, Net Prices, and Discounts for Branded Drugs in the US, 2007-2018. *JAMA*. 2020;323(9):854-862. doi:10.1001/jama.2020.1012.
3. Kang H, Lobo JM, Kim S, Sohn M-W. Cost-Related Medication Non-Adherence Among U.S. Adults With Diabetes. *Diabetes Res Clin Pract*. 2018;143:24-33. doi:10.1016/j.diabres.2018.06.016.
4. Horvath K, Jeitler K, Berghold A, et al. Long-Acting Insulin Analogues Versus NPH Insulin (Human Isophane Insulin) For Type 2 Diabetes Mellitus. *Cochrane Database of Systematic Reviews*. 2007;(2). doi:10.1002/14651858.CD005613.pub3.
5. Lipska KJ, Parker MM, Moffet HH, Huang ES, Karter AJ. Association of Initiation of Basal Insulin Analogs vs Neutral Protamine Hagedorn Insulin With Hypoglycemia-Related Emergency Department Visits or Hospital Admissions and With Glycemic Control in Patients With Type 2 Diabetes. *JAMA*. 2018;320(1):53-62. doi:10.1001/jama.2018.7993.
6. The Pharmacist's Letter. Comparisons of insulins. Therapeutic Research Center. 2017. December-Resource #331203. Available at: pharmacist.therapeuticresearch.com. Accessed April 20, 2020..
7. Peters, A. Insulin Short-Intermediate-Long. Wikimedia. Available at:https://commons.wikimedia.org/wiki/File:Insulin_short-intermediate-long_acting.svg. Accessed May 11, 2020.
8. Pharmacist's Letter. How to Switch Insulin Products. Therapeutic Research Center. 2019. August Resource #350802. Available at: pharmacist.therapeuticresearch.com. Accessed April 21, 2020.