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. Improving glycemic control in these patients has a substantial impact on reducing comorbidities 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. 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. 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. 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. However, the incidence of severe hypoglycemia with long-acting insulin analogs and NPH in patients with T2DM is similar. 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. 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. 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.

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. 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 Insulin

<table>
<thead>
<tr>
<th>Basal Insulin Product</th>
<th>Duration of Action</th>
<th>Dosing Interval</th>
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</thead>
<tbody>
<tr>
<td>NPH Insulin</td>
<td>Up to 24 hours</td>
<td>Once or twice daily</td>
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<tr>
<td>HUMULIN N</td>
<td>Up to 24 hours</td>
<td>Once or twice daily</td>
</tr>
<tr>
<td>Basal Insulin Analogs</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Insulin glargine (BASAGLAR, LANTUS)</td>
<td>Median 24 hours</td>
<td>Once daily</td>
</tr>
<tr>
<td>Insulin glargine U500 (TOUJEO)*</td>
<td>&gt; 24 hours</td>
<td>Once daily</td>
</tr>
<tr>
<td>Insulin detemir (LEVEMIR)</td>
<td>7.6 – 24 hours (dose-dependent)</td>
<td>Once or twice daily</td>
</tr>
<tr>
<td>Insulin degludec (TRESIBA)</td>
<td>At least 42 hours</td>
<td>Once daily at any time</td>
</tr>
</tbody>
</table>

* 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 Products

![Figure 1: Duration of Action of Insulin Products](image-url)
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.

**Table 2. Switching to or from NPH Insulin**

<table>
<thead>
<tr>
<th>Product Switch</th>
<th>Conversion</th>
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| Insulin detemir (LEVEMIR) to NPH | • Convert unit-per-unit*  
• Give NPH twice daily  
• 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 glargine U100 (LANTUS, BASAGLAR) or insulin glargine U300 (TOUJEO) to NPH | • 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 |
| Insulin degludec (TRESIBA) to NPH | |
| NPH insulin to insulin glargine U100 (LANTUS, BASAGLAR) or insulin glargine U300 (TOUJEO) | • 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) | • 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) | • Convert unit-per-unit and give once daily* |

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

**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*

**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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* 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
References:


