Effective Health Care

Clinician's Guide

Premixed Insulin Analogues

A COMPARISON WITH OTHER TREATMENTS FOR TYPE 2 DIABETES

Premixed insulin analogues are an option for treating adults with type 2 diabetes. This guide summarizes clinical evidence comparing the effectiveness and safety of premixed insulin analogues with other insulin preparations and oral diabetes drugs. This guide does not address the use of insulin in pumps. It does not address the effectiveness of insulin treatment for people with type 1 diabetes, women with gestational diabetes, or people younger than 18 years old. It also does not cover evidence about the effectiveness of dietary and other lifestyle modifications for treatment of type 2 diabetes.

Clinical Issue

Type 2 diabetes is a complex metabolic disorder characterized by insulin resistance in peripheral tissues and an inability of the pancreas to compensate by increasing insulin secretion.

Medication regimens to lower glucose levels are a primary component of type 2 diabetes treatment. Although oral diabetes drugs are often effective, insulin is frequently required to achieve a desired level of glucose control. Twenty-eight percent of people with type 2 diabetes use insulin alone or in combination with an oral diabetes drug.

Premixed insulin analogues combine rapid- and intermediate-acting insulin analogues and were developed to provide more flexibility in treatment regimens. They are among several treatment options when insulin is needed to treat type 2 diabetes.

We do not have enough data to compare premixed insulin analogues with all treatment options. However, there is sufficient evidence to compare them with premixed human insulin, long-acting insulin analogues, and oral diabetes drugs.

Clinical Bottom Line

- Premixed insulin analogues and premixed human insulin have similar effects on glycosylated hemoglobin (A1c), and rates of hypoglycemia are similar.

  LEVEL OF CONFIDENCE ● ● ●

- Premixed insulin analogues help achieve lower postprandial glucose levels than premixed human insulin.

  LEVEL OF CONFIDENCE ● ● ●

- Premixed insulin analogues help achieve lower A1c levels than long-acting insulin analogues used alone, but rates of hypoglycemia are higher.

  LEVEL OF CONFIDENCE ● ● ●

- Premixed insulin analogues are linked with more episodes of hypoglycemia than oral diabetes drugs.

  LEVEL OF CONFIDENCE ● ● ●

- Premixed insulin analogues help achieve lower A1c levels than oral diabetes drugs used alone.

  LEVEL OF CONFIDENCE ● ● ○

CONFIDENCE SCALE

The confidence ratings in this guide are derived from a systematic review of the literature. The level of confidence is based on the overall quantity and quality of clinical evidence.

HIGH ● ● ● There are consistent results from good quality studies. Further research is very unlikely to change the conclusions.

MEDIUM ● ● ○ Findings are supported, but further research could change the conclusions.

LOW ● ○ ○ There are very few studies, or existing studies are flawed.

SOURCE The source material for this guide is a systematic review of 45 research studies. The review, *Comparative Effectiveness, Safety, and Indications of Insulin Analogues in Premixed Formulations for Adults With Type 2 Diabetes* (2008), was prepared by the Johns Hopkins Evidence-based Practice Center. The Agency for Healthcare Research and Quality (AHRQ) funded the systematic review and this guide. The guide was developed using feedback from clinicians who reviewed preliminary drafts.

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Insulin Preparations

Insulin preparations (Table 1) are distinguished by their pharmacokinetic properties, including onset, peak, and duration of action (Figure 1).

Human Insulin

Recombinant human insulin is structurally identical to insulin produced by the human pancreas. Human insulin is available in short-acting (regular insulin) and intermediate-acting (NPH insulin) preparations.

- Regular insulin injected subcutaneously enters the bloodstream more slowly and over a longer period of time than insulin secreted by the pancreas in response to a meal.
- NPH insulin enters the bloodstream more slowly than regular insulin, and its levels rise and fall over a longer period of time.

Premixed Human Insulin

Premixed combinations of NPH and regular insulin are available. They provide basal (continuous) insulin supplementation and short-term mealtime coverage.

Insulin Analogues

Insulin analogues are modified forms of human insulin. Amino acid substitutions alter their pharmacokinetic properties.

- Lispro, aspart, and glulisine have a more rapid onset and shorter duration of action than regular insulin. Like regular insulin, they are taken at mealtimes.
- Glargine and detemir have a longer duration of action and maintain more constant blood levels than NPH insulin.

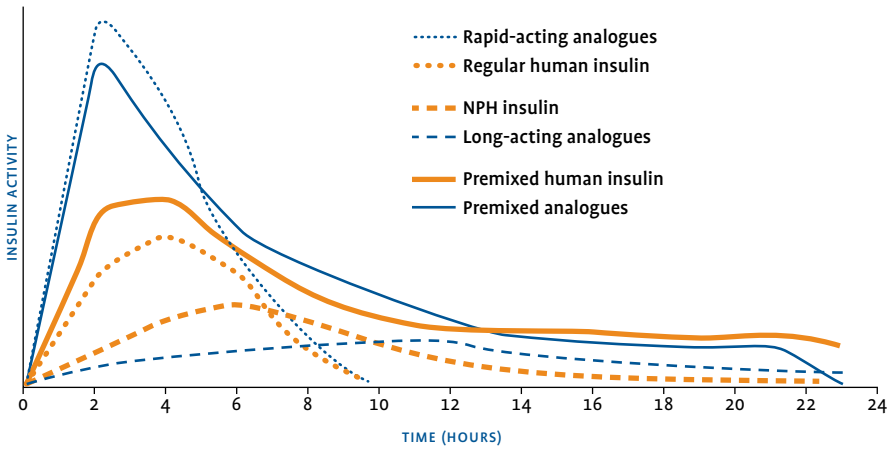
Premixed Insulin Analogues

Premixed insulin analogues combine a rapid-acting insulin analogue with its intermediate-acting protamine suspension. They provide basal insulin supplementation and short-term mealtime coverage.

Table 1. Insulin Preparations

Drug Name	Brand Name
RAPID-ACTING INSULIN ANALOGUES	
Insulin aspart	NovoLog®
Insulin glulisine	Apidra®
Insulin lispro	Humalog®
SHORT-ACTING INSULIN	
Regular insulin	Humulin® R Novolin® R
INTERMEDIATE-ACTING INSULIN	
NPH insulin	Humulin® N Novolin® N
LONG-ACTING INSULIN ANALOGUES	
Insulin detemir	Levemir®
Insulin glargine	Lantus®
PREMIXED HUMAN INSULIN	
NPH/regular insulin	Humulin® 70/30 Novolin® 70/30 Humulin® 50/50
PREMIXED INSULIN ANALOGUES	
Insulin aspart protamine suspension/ insulin aspart	NovoLog® Mix 70/30
Insulin lispro protamine suspension/ insulin lispro	Humalog® Mix75/25 Humalog® Mix50/50

Figure 1. Activity of Insulin Preparations



Adapted from product label information approved by the Food and Drug Administration.

Comparing Effectiveness and Adverse Events

The evidence compiled for this guide (Table 2) comes primarily from clinical studies that compare premixed insulin analogues with other insulin preparations or oral diabetes drugs.

The main outcomes in these studies were intermediate measures of clinical effectiveness, including A1c, fasting glucose, and postprandial glucose.

The studies were not designed to assess cardiovascular outcomes or morbidity.

There is not enough evidence to compare premixed insulin analogues with rapid-acting insulin analogues alone, NPH insulin alone, or regimens using both short-acting and long- or intermediate-acting insulin in other dosing ratios.

In general, premixed insulin analogues:

- Lead to lower postprandial glucose levels than premixed human insulin; other outcomes are similar.
- Lead to lower A1c and postprandial glucose levels than long-acting insulin, but higher fasting glucose.
- Lead to lower A1c and glucose levels than oral diabetes drugs.

Table 2. Comparing **Three Diabetes Treatments** With **Premixed Insulin Analogues**

	COMPARING		COMPARING		COMPARING	
	Oral Drugs for Diabetes	Premixed Analogues	Long-Acting Analogues	Premixed Analogues	Premixed Human Insulin	Premixed Analogues
MORE EFFECTIVE						
Better at lowering A1c		✔		✔	Similar results	
Better at lowering fasting glucose		✔	✔		Similar results	
Better at lowering postprandial glucose		✔		✔		✔
FEWER ADVERSE EVENTS						
Lower rates of hypoglycemia[1]	✔		✔		Similar results	
Less weight gain	✔		✔		Similar results	

[1] Symptomatic episodes that were self-treated and not severe enough to require intervention by another person.

✔ = more effective than the comparator with Level of Confidence ●●● or ●●○.

Choosing Types of Insulin

Selecting the type of insulin preparation depends on many factors, including an individual's response to insulin, meal patterns, ability to self-inject, diet, exercise, and preferences. Also, insulin preparations vary in their effectiveness to control fasting and postprandial glucose levels.

Controlling both fasting and postprandial glucose levels is necessary to achieve glycemic control. At higher A1c levels, fasting glucose control is more beneficial in lowering A1c closer to the desired target of about 7 percent. When A1c is closer to 7 percent, postprandial glucose control becomes more important.

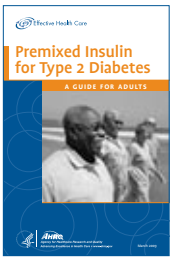
- For people who have not achieved adequate glucose control on oral diabetes drugs, insulin therapy should be considered.
- Premixed insulin analogues and premixed human insulin have similar effects on A1c and fasting glucose. However, premixed insulin analogues lead to lower postprandial glucose levels.
- Premixed insulin preparations are intended to simplify dosing and may permit a lower number of daily insulin injections for people using more than one type of insulin.
- Premixed insulin preparations are available in 70/30, 75/25, and 50/50 ratios for basal supplementation and mealtime coverage.
- Premixed insulin preparations are not as suitable as single insulin formulations for adjusting daily doses to account for changes in activity levels and meal regimens.

On the Horizon

A retrospective observational study comparing the cardiovascular outcomes of people starting insulin glargine compared with those starting premixed insulin analogues was completed in January 2008.

Two additional studies are in progress to evaluate quality of life and treatment satisfaction with premixed insulin analogues and the long-acting insulin glargine with or without rapid-acting glulisine.

Resource for Patients



Premixed Insulin for Type 2 Diabetes: A Guide for Adults is a companion to this Clinician's Guide. It can help people talk with their health care professional about insulin. It provides information about:

- Types of insulin.
- Benefits, risks, and price of insulin preparations.
- Seeking advice from a health care professional about insulin options.

For More Information

For electronic copies of the consumer's guide, this clinician's guide, and the full systematic review, visit this Web site: **www.effectivehealthcare.ahrq.gov**

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Still Unknown

Evidence is insufficient to determine whether the effectiveness or adverse events of premixed insulin analogues vary by age, gender, race, or ethnicity. Evidence is also insufficient to determine if they vary for people with poor glycemic control or coexisting medical conditions.

There is also insufficient evidence on the long-term safety of premixed insulin analogues and their impact on quality of life and treatment satisfaction.

Most studies of premixed insulin analogues last 1 year or less and focus on short-term outcomes. Therefore, evidence is insufficient to determine the effects of premixed insulin analogues on long-term outcomes, such as mortality, cardiovascular disease, kidney disease, neuropathy, retinopathy, and long-term weight change, compared with other antidiabetic medications.

Price of Insulin

Drug Name[1]	Brand Name	Price[2] One Vial (1,000 units)	Price[2] Five-Pack Pens (1,500 units)
RAPID-ACTING INSULIN ANALOGUES			
Insulin aspart	NovoLog®	$105	$200
Insulin glulisine	Apidra®	$95	$180
Insulin lispro	Humalog®	$105	$200
SHORT-ACTING INSULIN			
Regular insulin	Humulin® R	$45	NA
	Novolin® R	$45	$135
INTERMEDIATE-ACTING INSULIN			
NPH insulin	Humulin® N	$45	$135
	Novolin® N	$45	$135
LONG-ACTING INSULIN ANALOGUES			
Insulin detemir	Levemir®	$95	$190
Insulin glargine	Lantus®	$95	$190
PREMIXED HUMAN INSULIN			
70% NPH/30% regular insulin	Humulin® 70/30	$45	$135
	Novolin® 70/30	$45	$135
50% NPH/50% regular insulin	Humulin® 50/50	$45	NA
PREMIXED INSULIN ANALOGUES			
70% insulin aspart protamine suspension/30% insulin aspart	NovoLog® Mix 70/30	$105	$200
75% insulin lispro protamine suspension/25% insulin lispro	Humalog® Mix75/25	$105	$200
50% insulin lispro protamine suspension/50% insulin lispro	Humalog® Mix50/50	$105	$200

[1] These drugs were evaluated in the systematic review.
[2] Average Wholesale Price from *Red Book*, 2008. Price does not include cost of needles or syringes.
NA = not available in pens.

AHRQ created the John M. Eisenberg Center at Oregon Health & Science University to make research useful for decisionmakers. This guide was written by Monica Goei, M.D., David Hickam, M.D., Joe Stewart, B.C.N.S.P., Martha Schechtel, R.N., Seth Meyer, M.A., Rachelle Nicolai, B.A., and Valerie King, M.D., of the Eisenberg Center.

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