New England Comparative Effectiveness Public Advisory Council

Public Meeting – Providence, Rhode Island
Controversies in the Management of Patients with Type 2 Diabetes
October 29, 2014
Voting Questions for Management Options for Type 2 Diabetes

Introduction to CEPAC's Votes

Each public meeting of CEPAC involves deliberation and voting on key questions related to the systematic review of the evidence presented by ICER. Members of CEPAC will discuss issues regarding the application of the available evidence to guide clinical decision-making and payer policies. ICER develops the key questions with significant input from members of the CEPAC Advisory Board to ensure that the questions are framed to address the issues that are most important in applying the evidence to practice and medical policy decisions.

About the Questions

Comparative Clinical Effectiveness

The general framework within which CEPAC discusses and votes on the evidence is shown below:

Given a health care "intervention A" for "patients with condition X," we will compare its clinical effectiveness for these patients to that of a "comparator B" by voting on the following question:

Is the evidence "adequate" to demonstrate that "intervention A" is equivalent or superior to "comparator B" for "patients with condition X"?

Discussion and voting will highlight the following issues:

1. The evidence on risks and benefits to determine the *comparative* clinical effectiveness of management options for specific patient populations. In judging comparative clinical

effectiveness, there are two interrelated questions: the relative magnitude of differences in risks and benefits; and the relative confidence that the body of evidence can provide in the accuracy of estimates of risks and benefits. Considering these two issues together is required in order to make a judgment of whether the evidence is "adequate" to demonstrate that one intervention is equivalent to or superior than another.

2. Issues related to individual patient preferences and values, provider training, volume, or other factors that should be considered in judging the evidence on clinical effectiveness and value.
3. Weighing the evidence on cost-effectiveness and projected budgetary impact to determine the comparative value of various management options for key patient populations.
4. Comments or recommendations related to broader considerations of public health, equity, disparities, and access.

Comparative Value

When a majority of CEPAC votes that the evidence is adequate to demonstrate that an intervention produces patient outcomes equivalent or superior to a comparator, the Council will also vote on whether or not the intervention, care management program, or other health system innovation represents a "high," "reasonable," or "low" value. For those Council members who vote that the evidence is inadequate to demonstrate that one intervention produced patient outcomes equivalent or superior to another, ICER will automatically designate these as a "low" value vote. Typically, the value "perspective" that CEPAC will be asked to assume is that of a state Medicaid program or a provider group that must make resource decisions within a fixed budget for care. While information about hypothetical budget tradeoffs are provided, CEPAC will not be given prescribed boundaries or thresholds for budget impact or incremental cost-effectiveness ratios to guide its judgment of high, reasonable, or low value. When voting on value, CEPAC will grade their votes according to the different categories on the following page to explain their rationale for determining one intervention to have "high", "reasonable", or "low" comparative value to another.

Table 1. Value Voting Categories

Low Value	Reasonable/Comparable Value	High Value
1. Worse outcomes; Higher or equivalent cost	5. Worse outcomes; Lower cost	9. Comparable outcomes; Lower cost
2. Comparable outcomes; Higher costs	6. Comparable outcomes; Comparable cost	10. Promising but inconclusive evidence of better outcomes; Lower cost
3. Promising but inconclusive evidence of better outcomes; Higher cost	7. Promising but inconclusive evidence of better outcomes; Comparable cost	11. Better outcomes; Lower or comparable cost
4. Better outcomes; Too high a cost	8. Better outcomes; Reasonable higher cost	12. Better outcomes; Slightly higher cost

Voting Questions – Management Options for Type 2 Diabetes

Comparative Clinical Effectiveness and Comparative Value

Insulin choice for adjunctive therapy:

Human insulin vs. insulin analogs

1. Is the evidence adequate to demonstrate that ***NPH insulin*** (intermediate-acting human insulin) is functionally equivalent to ***long-acting insulin analogs*** for most patients with type 2 diabetes?

2. If yes, from the perspective of a state Medicaid program, would you judge the value of ***NPH insulin*** compared to ***long-acting insulin analogs*** to be:

   1) high; 2) reasonable; or 3) low?

Second-line pharmacotherapy options for patients with inadequate glycemic control from metformin monotherapy:

Combination therapy with Metformin plus DPP-4 inhibitor or sulfonylurea

3. Is the evidence adequate to demonstrate that combination therapy with ***metformin + DPP-4 inhibitor*** is superior to ***metformin + sulfonylurea*** for most patients with type 2 diabetes for whom metformin monotherapy provides inadequate glycemic control?

4. If yes, from the perspective of a state Medicaid program, would you judge the value of ***metformin+ DPP-4 inhibitor*** compared to ***metformin + sulfonylurea*** to be:

   1) high; 2) reasonable; or 3) low?

Combination therapy with Metformin plus GLP-1 receptor agonist or sulfonylurea

5. Is the evidence adequate to demonstrate that combination therapy with ***metformin + GLP-1 receptor agonist*** is superior to ***metformin + sulfonylurea*** for most patients with type 2 diabetes for whom metformin monotherapy provides inadequate glycemic control?

6. If yes, from the perspective of a state Medicaid program, would you judge the value of ***metformin + GLP-1 receptor agonist*** compared to ***metformin + sulfonylurea*** to be:

   1) high; 2) reasonable; or 3) low?

Third-line pharmacotherapy options for patients with inadequate glycemic control from metformin combination therapy with sulfonylurea:

Combination therapy with Metformin plus sulfonylurea + either DPP-4 inhibitor or insulin

7. Is the evidence adequate to demonstrate that combination therapy with ***metformin + sulfonylurea + DPP-4 inhibitor*** is superior to ***metformin + sulfonylurea + NPH insulin*** for most patients with type 2 diabetes with inadequate glycemic control?

8. If yes, from the perspective of a state Medicaid program, would you judge the value of ***metformin + sulfonylurea + DPP-4 inhibitor*** compared to ***metformin + sulfonylurea + NPH insulin*** to be:

   1) high; 2) reasonable; or 3) low?

Combination therapy with Metformin plus sulfonylurea + either GLP-1 receptor agonist or insulin

9. Is the evidence adequate to demonstrate that combination therapy with ***metformin + sulfonylurea + GLP-1 receptor agonist*** is equivalent or superior to ***metformin + sulfonylurea + NPH insulin*** for most patients with type 2 diabetes with inadequate glycemic control?

10. If yes, from the perspective of a state Medicaid program, would you judge the value of ***metformin + sulfonylurea + GLP-1 receptor agonist*** compared to ***metformin + sulfonylurea + NPH insulin*** to be:

    1) high; 2) reasonable; or 3) low?

Insulin delivery:

Insulin pumps vs. multiple daily injections

11. Is the evidence adequate to demonstrate that any clinical subpopulation of patients with type 2 diabetes does better with ***insulin pumps*** compared to ***multiple daily injections***?

Glucose monitoring:

Self-monitoring of blood glucose vs. Continuous glucose monitors

12. Is the evidence adequate to demonstrate that any clinical subpopulation of patients with type 2 diabetes does better with ***continuous glucose monitors*** compared to ***self-monitoring of blood glucose***?

Broader considerations for public health and disparities

13. Are there any considerations related to public health, equity, disparities in access or outcomes for specific patient populations, or other social values that should also be considered in medical policies related to the use of pharmacotherapy treatment options, insulin delivery systems, or glucose monitoring methods and devices in patients with type 2 diabetes?

Definitions

1) **Continuous glucose monitors:** devices that use sensors applied subcutaneously to measure and record blood glucose levels in real time throughout the day and signal an alarm if blood sugar concentration is too high or too low as an alternative to self-monitoring or conventional glucose monitors.

2) **DPP-4 inhibitors:** also known as gliptins, DPP-4s are a relatively new class of oral anti-hyperglycemic medications, first approved by the FDA in 2006. These drugs work by interrupting DPP-4 enzymes, which destroy beneficial GLP-1 hormones, thereby allowing GLP-1 hormones to promote the release of insulin and the suppression of glucagon. Several DPP-4 agents are available, including sitagliptin (Januvia®, Merck & Co.), saxagliptin (Onglyza®, Bristol-Meyers Squibb Company) and linagliptin (Tradjenta®, Boehringer Ingelheim Pharmaceuticals).

3) **GLP-1 receptor agonists:** GLP-1 receptor agonists are part of new group of injectable drugs that control blood glucose with three different mechanisms: 1) by mimicking natural GLP-1 hormones to increase insulin secretion; 2) by suppressing pancreatic glucagon secretion (glucagon typically raises blood glucose levels); and 3) by slowing gastric emptying, or the passage of food from the stomach to the small intestine. Available versions of GLP-1 include exenatide (Byetta® and Bydureon®, Bristol-Meyers Squibb Company; Bydureon Pen ®, AstraZeneca plc) and liraglutide (Victoza®, Novo Nordisk A/S).

4) **Inadequate glycemic control:** typically defined as a glycosolated hemoglobin (HbA1c) concentration consistently greater than 7% despite the use of oral antidiabetic agents and/or insulin. The use of a specific threshold to define glycemic control is currently a subject of intense debate, but 7% remains a common goal for most patients.

5) **Insulin pumps:** Insulin pumps are small devices that can be programmed to provide both continuous doses of insulin throughout the day and/or fast-acting doses around meal time through a catheter. Pumps are designed to improve patient convenience and glycemic control, and minimize the need for multiple daily injections of insulin. A variety of insulin pumps are available, each with different technological features and accompanying supplies, including tubing, cartridges, dressing, and syringes.

6) **Long-acting insulin analogs:** Insulin analogs involve molecularly altered insulin to allow for more predictable cell absorption compared to human formulations. Long-acting insulin analogs are used in those who seek consistent blood glucose levels throughout the day, and are used once or twice daily. Available versions include Insulin detemir (Levemir®, Novo Nordisk, A/S) and Insulin glargine (Lantus®, Sanofi US, Inc.).

7) **Metformin:** an oral antidiabetic medication within the biguanide drug class, metformin decreases hepatic glucose production, decreases intestinal absorption of glucose, and improves insulin sensitivity by increasing peripheral glucose uptake and utilization. Taken alone or in combination with other antidiabetic medications, metformin is widely accepted as an appropriate first-line medication for type 2 diabetes.

8) **Most patients with type 2 diabetes:** certain patient populations may not be candidates for some of the therapeutic alternatives under consideration. For example, any patient at elevated risk of hypoglycemia, such as the very elderly, should avoid those agents known to increase the risk (e.g., NPH insulin, sulfonylureas). Patients with impaired renal function should avoid sulfonylureas. Those with a history of pancreatitis may need to avoid GLP-1 agonists or DPP-4 inhibitors. Very obese patients should avoid agents known to increase body weight (i.e., insulins, sulfonylureas).

9) **Multiple daily injections:** An approach to diabetes management that involves injecting long- or intermediate-acting insulin once or twice daily, in addition to fast-acting insulin around each meal time.

10) **NPH insulin**: neutral protamine Hagedorn, an intermediate-acting human insulin applied once or twice daily to help lower blood glucose levels in patients with diabetes. Insulin mimics the normal release of natural insulin from pancreatic beta cells in patients with uncontrolled hyperglycemia Also known as Humulin N® (Eli Lilly and Company) and Novolin N® (Novo Nordisk, A/S). Human synthetic insulin, unlike insulin analogs, is based on recombinant human DNA and therefore identical to the structure of natural insulin.

11) **Self-monitoring of blood glucose:** pricking the finger using a lancet and test strips to manually determine the concentration of glucose in a sample of blood

12) **Sulfonylureas:** Oral antidiabetic medications that work by binding to channels on pancreatic cells, increasing the release of insulin from the pancreas to control blood glucose levels. Sulfonylureas are available in a number of generic and branded forms, and include different generations of agents. Sulfonylureas are generally used at earlier stages of the condition, given their reliance on functioning beta cells in the pancreas to stimulate the release of insulin.