

# Managing the Evolving Complexity of Pharmacologic Treatment: Comparative Effectiveness Research, Pharmacoeconomic Data Analyses, and Other Decision Support Tools

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## Abstract

Eleven classes of antidiabetic medicines are now available to help the 25.8 million Americans with type 2 diabetes control their blood sugar levels when diet and lifestyle modifications are not sufficient. Although patients benefit from the myriad of treatment options, there are little comparative data to effectively differentiate the products and predict their relative utility. In the absence of true comparative outcomes data, comparative effectiveness research (CER) provides a valuable tool to compare the safety and efficacy of agents and applies the results to heterogeneous patient populations, including patients ordinarily excluded from randomized controlled trials. Thus, CER provides more generalizable results that better reflect real-world situations faced by practitioners and patients. In addition to traditional CER approaches such as systematic reviews, meta-analyses, and retrospective claims analyses, Markov modeling and Bayesian analysis can be applied to predict patient outcomes in scenarios in which clinical trials are not feasible. CER may be the best way to consolidate and interpret data on the many agents involved and thereby guide rational treatment decisions.

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For author information and disclosures, see end of text.

## Comparative Effectiveness Research

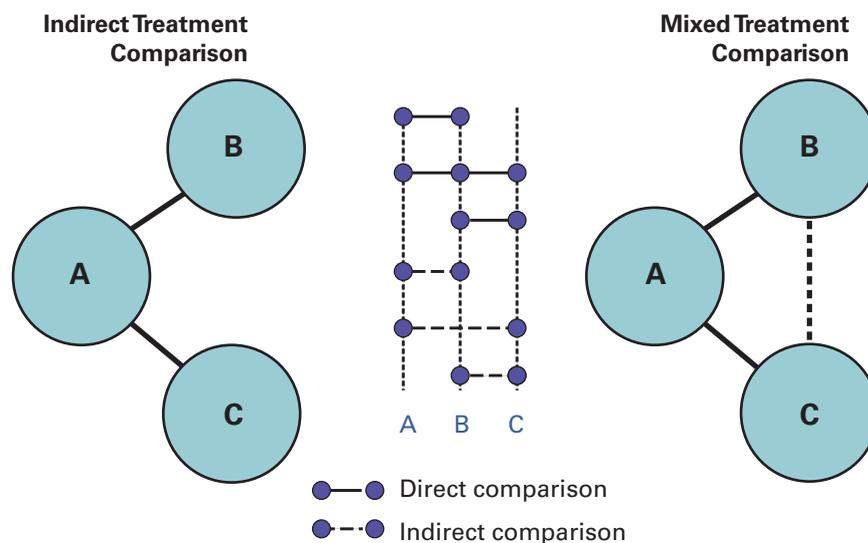
Comparative effectiveness research (CER) is defined by the Institute of Medicine as the generation and synthesis of evidence that compares the benefits and harms of alternative methods to prevent, diagnose, treat, and monitor a clinical condition, or to improve the delivery of care.<sup>1</sup> CER takes perspectives from across the continuum of care and uses them to support patient-centric decision making in specific populations to improve treatment outcomes.<sup>1</sup> In addition to traditional CER approaches, such as systematic reviews, meta-analyses, and retrospective claims analyses, Markov modeling and Bayesian analysis can be applied to predict patient outcomes in scenarios in which clinical trials are not feasible.

Historically, healthcare providers and policy makers have relied on randomized controlled clinical trials (RCTs) to determine the efficacy of medications. Although effective for addressing regulatory questions, RCTs and their placebo comparators, surrogate measures of disease improvement, strict inclusion/exclusion criteria, high adherence, and routine monitoring of patients are inherently limited when it comes to addressing the effectiveness of a treatment. Effectiveness is better measured under real-world conditions in which a variety of patients who typically do not meet the entry criteria for an RCT are treated with the agent. In the real world, a specific drug is often used after a series of treatment failures or may be taken in combination with other prescribed and over-the-counter therapies not permitted in the RCT. Patients in the real world often fail to take their medication exactly as prescribed and rarely receive the intensity of follow-up and monitoring common in an RCT. CER is designed to evaluate whether products are safe and effective for use in heterogeneous patient populations ordinarily excluded from RCTs, and its results can be applied to real-world situations faced by practitioners and patients.

## Direct, Indirect, and Mixed Treatment Comparisons

Physicians, payers, and policy makers rely on direct or head-to-head comparisons of therapies when making treatment and coverage decisions. However, evidence that directly compares a treatment of interest with all competing therapies is often not available.<sup>2</sup> When direct comparisons are lacking, decision makers are forced to rely on indirect treatment comparisons. An indirect treatment comparison

■ **Figure 1.** Schematic of an Indirect Treatment Comparison<sup>3</sup>



If trials A + B and A + C have comparable effects on the dependent variable, then an unbiased indirect estimate for the relative effect of C versus B can be obtained from the estimates of the effect of B versus A and the effect of C versus A.  
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is illustrated in the left-hand panel of **Figure 1**. If 2 particular treatments (B and C) have never been compared in a head-to-head trial, but these 2 treatments have been compared with a common comparator (A), then it may be appropriate to base an indirect comparison of B and C on the direct comparison of B and A and the direct comparison of A and C.<sup>3</sup> Results of an indirect treatment comparison can provide useful evidence of the difference in treatment effects among competing interventions and can aid in selecting the best choice of treatment.

Even when the results of the head-to-head or direct comparison are conclusive, combining them with the results of indirect estimates in a mixed treatment comparison may yield a more precise estimate of the effectiveness or safety of the interventions in question and broaden inference to the population sampled. As illustrated in the right-hand panel of **Figure 1**, a mixed treatment comparison links existing information within the network of treatment comparisons.<sup>4,5</sup>

### Network Analysis

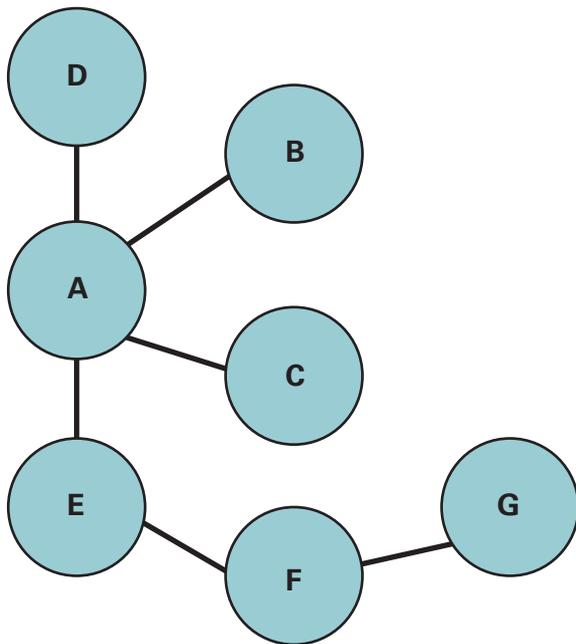
In a traditional meta-analysis, all included studies compare a treatment of interest with the same comparator. Network meta-analysis extends this concept by including comparisons across a range of interventions and provides estimates of relative treatment effects on multiple treatment comparisons.<sup>3</sup> A network analysis starts with a network of evidence that includes the relevant treatments and the clinical

cal trials that have compared those treatments directly. Each node of the network represents a treatment, and each link connects treatments that have been directly compared in 1 or more RCTs.<sup>3</sup> For example, in **Figure 2**, interventions B, C, D, and E are all “anchored” on the common comparator A, but interventions F and G are not. However, because these interventions are all connected in the network (ie, each pair has a path from one to the other), an indirect comparison of each intervention with any other is possible (although comparisons with longer paths will have less precision).<sup>3</sup> In essence, network meta-analysis is a means of estimating relative treatment effects between competing interventions for comparative effectiveness purposes.

### Bayesian Analysis

Another approach to synthesizing data for use in CER is via Bayesian analysis. When existing data are limited or clinical trials are not feasible, Bayesian techniques can be used to synthesize new data to include in the CER analysis.<sup>6</sup> Bayesian methods utilize existing data on treatment outcomes to calculate the probability or likelihood of a future outcome. These probabilities provide a straightforward way to make predictions about treatment effects, even when direct clinical trial data are noninformative or missing.<sup>2</sup> A particular strength of the Bayesian approach is that it considers all evidence, including unanticipated evidence, as it becomes available. In other words, data reflecting the most current state of knowl-

■ **Figure 2.** An Example of a Network of Clinical Trials Connected via Common Comparators<sup>3</sup>



In this network, not all trials have a common comparator, but all interventions are still connected. The F and G interventions are connected with A, B, C, D, and E by the EF trials and the FG trials, thus making indirect comparisons of each intervention with any other possible. Reprinted with permission from Jansen JP, Fleurence R, Devine B, et al. *Value Health*. 2011;14(4):417-428.

edge can be integrated into a Bayesian model to predict the likelihood that the results of a hypothetical clinical trial (eg, a head-to-head trial) conducted at some point in the future will fall within a certain range. This predictive capacity of Bayesian analysis can be particularly beneficial to pharmacy decision makers when head-to-head clinical trial data to guide therapeutic decision making are unavailable. Because a Bayesian model can continually update probability distributions as real clinical trial data are generated, it is particularly well suited for CER.<sup>7</sup>

### CER Analysis of Antidiabetic Therapies

Eleven classes of medications are now approved by the US Food and Drug Administration for treating patients with type 2 diabetes mellitus (T2DM). Although patients may benefit from the increased number of options, clinicians are challenged to select the most appropriate treatment regimen. Furthermore, patients often require 2 or more medications that target different dysfunctional organs to achieve glycemic control.<sup>8</sup> With the number of antidiabetic agents continuing

to increase, an evaluation comparing the efficacy and safety of these agents is needed; however, these data are often lacking. In the absence of true comparative data, CER provides a viable tool to assess the efficacy of competing treatment options across a chronic disease like diabetes.<sup>9,10</sup>

Data used in CER come from systematic reviews of existing placebo-controlled clinical trials, meta-analyses, retrospective claims analyses, and patient data sets.<sup>9,10</sup> For example, a comparative analysis of antidiabetic agents was performed by the Agency for Healthcare Research and Quality (AHRQ) in 2007.<sup>11</sup> This analysis sourced data from 216 published studies and assessed differences in efficacy and safety of oral antidiabetic drugs across patient populations defined by race, ethnicity, sex, and age. The impact of these agents on comorbid conditions and humanistic outcomes, such as quality of life, was also evaluated.<sup>4</sup> Shortly after the 2007 CER was published, the first of the incretins, a class of antidiabetic agents that includes the orally available dipeptidyl peptidase-4 (DPP-4) inhibitors and injectable glucagon-like peptide-1 (GLP-1) agonists, gained regulatory approval. As with most new therapies, there were little clinical trial data that compared these novel agents with existing therapies. To address this need, the AHRQ published a follow-up CER that utilized published data to synthesize head-to-head comparisons of monotherapy with metformin, thiazolidinediones (TZDs), second-generation sulfonylureas, DPP-4 inhibitors, meglitinides, and GLP-1 agonists. It also compared the safety and efficacy of recently introduced therapeutic combinations, including metformin plus a DPP-4 inhibitor and a TZD plus meglitinide.<sup>12,13</sup>

Briefly, results of the 2011 CER indicated similar absolute reductions in glycated hemoglobin (A1C) levels versus baseline (approximately 1%) for most monotherapies, including the incretins.<sup>12</sup> Adding a second agent lowered A1C levels by an additional 1%; however, most 2-drug combinations demonstrated similar reductions in A1C level.<sup>13</sup> Premixed insulin analogues were more effective in lowering fasting glucose levels compared with long-acting insulin analogues and noninsulin oral antidiabetic drugs. Unlike most medications, oral metformin and injectable GLP-1 agonists were not associated with weight gain. Metformin had a greater effect on body weight than other oral drugs, with a mean difference in weight change ranging from 1.4 to 2.7 kg.<sup>12</sup>

The most common adverse events were hypoglycemia, most notably with sulfonylureas, and gastrointestinal events, especially with metformin. Sulfonylureas had a 4-fold higher risk of mild-to-moderate hypoglycemia compared with metformin monotherapy. This risk increased when sulfonylureas were combined with metformin. TZDs demonstrated a higher

risk for congestive heart failure compared with sulfonylureas and an increased risk for bone fractures versus metformin. Diarrhea occurred more often with metformin compared with TZDs.<sup>13</sup>

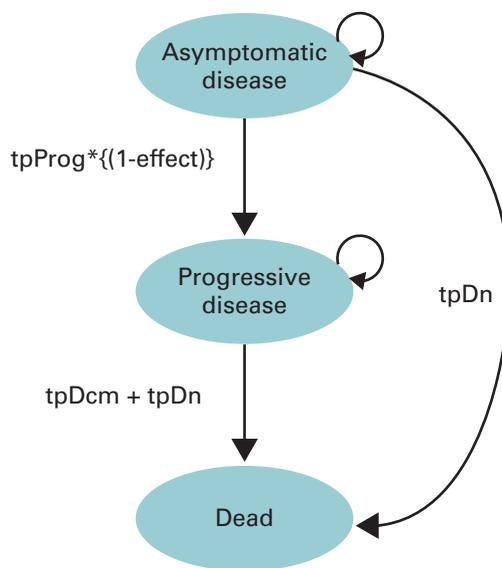
Although the updated 2011 AHRQ CER review of antidiabetic agents included additional data on existing and recently approved agents, there remains a need for additional data describing the comparative efficacy of approved antidiabetic medications.

### Assessing Cost-Effectiveness With Markov Modeling

Assessing the cost-effectiveness of a therapy often requires modeling to estimate the impact of the intervention on cost, survival, and quality of life over time. Markov modeling has become the standard approach for predicting long-term clinical and economic outcomes.<sup>14</sup> A Markov model considers patients in a discrete state of health, for example, healthy, ambulatory, ill, or hospitalized. Using transition probabilities determined from epidemiological or clinical studies in the literature, the model predicts the movement of patients from one state of health to another (eg, from healthy to hospitalized) over time (Figure 3). Running the model for several cycles provides an estimate of the long-term health outcomes or costs associated with a disease or a particular intervention.<sup>14</sup>

A validated Markov model developed by the Center for Outcomes Research (CORE) was used by Premera Blue Cross to determine the budgetary impact of adding the GLP-1 agonist exenatide to its formulary.<sup>15</sup> This model incorporated widely recognized surrogate clinical end points such as A1C level, low-density lipoprotein cholesterol level, and body mass index to project long-term clinical end points such as myocardial infarction, stroke, end-stage renal disease, neuropathy, and retinopathy. Future versions of the CORE model will incorporate additional biomarkers of beta cell function and glucose homeostasis as they are identified and validated. The model also projected economic end points, including drug cost, total cost of care, life expectancy, and quality-adjusted life-years (QALYs).<sup>15</sup> The Premera pharmacy plan administrators were interested in estimating the cost-effectiveness of GLP-1 agonist treatment in a standard cohort of patients with T2DM compared with a modified obese cohort that was otherwise demographically similar at baseline. The model was designed to compare projected treatment complications and their associated costs in patients treated with a GLP-1 agonist and other antidiabetic agents over a 30-year time horizon.<sup>15</sup> Model outputs demonstrated that treatment with a GLP-1 agonist was more cost-effective over the 30-year window in

■ **Figure 3.** Example of a 3-State Markov Model<sup>14</sup>



Each oval represents a possible disease state. The arrows represent possible transitions between those states. Effect indicates effectiveness of drug in reducing disease progression; tpDcm, transition probability to death as a direct result of the disease; tpDn, transition probability to natural death; tpProg, transition probability to progression. Reprinted with permission from Briggs A, Sculpher M. *Pharmacoeconomics*.1998;13(4):397-409.

this cohort of obese patients with diabetes when compared with pioglitazone and insulin glargine. It did not show better cost-effectiveness versus metformin because of the low acquisition cost of metformin. The authors concluded that this case illustrated how disease-based economic models could inform a formulary review process by predicting potential reductions in overall cost burden and suggesting subpopulations in which the drug might have greater impact. However, they cautioned that both the developer of the model and end users of the model outputs should be aware of the inherent limitations of projecting long-term outcomes from short-term data.<sup>15</sup>

Recently, the CORE Markov model was utilized to estimate the clinical and economic benefits of treatment with extended-release exenatide compared with sitagliptin or pioglitazone in a hypothetical population of 1000 American patients with diabetes on a preexisting regimen of metformin and/or sulfonylurea.<sup>16</sup> Baseline patient characteristics and clinical data from a phase 3 clinical trial that compared once-weekly exenatide with sitagliptin or pioglitazone were used in the model. Treatment-related complication costs were extracted from published sources. At 6 months, patients treated with once-weekly exenatide had greater improvements in A1C level and body weight than those

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treated with sitagliptin or pioglitazone.<sup>16</sup> Over the 35-year time horizon, once-weekly administration of exenatide increased life expectancy and QALYs compared with sitagliptin or pioglitazone. Once-weekly exenatide was also associated with lower lifetime complication costs, primarily due to lower projected cumulative incidence of cardiovascular diseases and neuropathic complications.<sup>16</sup>

The CORE Markov model has also been used to evaluate the long-term cost-effectiveness of once-daily liraglutide (versus twice-daily exenatide) combined with metformin, glimepiride, or both for the treatment of T2DM in 1000 simulated patients.<sup>17</sup> Data from the LEAD (Liraglutide Effect and Action in Diabetes)-6 trial, a phase 3, open-label, active comparator, head-to-head trial of liraglutide versus exenatide for 26 weeks, were incorporated into the model.<sup>18</sup> Results generated by the Markov model indicated that projected over a 35-year time horizon, lifetime treatment costs were higher for liraglutide, but costs of diabetes-related complications were lower versus exenatide.<sup>17</sup> Additionally, liraglutide was associated with an increase in both life expectancy and QALYs.<sup>17</sup> With the caveat that short-term clinical data may not accurately or fully predict long-term outcomes, this analysis suggests that liraglutide in combination with metformin and glimepiride appeared to be cost-effective in a US payer setting over a 35-year time horizon.<sup>17</sup>

## Conclusion

Physicians, policy makers, and payers need robust evidence to support healthcare decision making. By drawing on existing data, CER provides a tool to view all available evidence describing the risks and benefits of each therapeutic choice. Ideally, data from RCTs are available to inform all policy and patient care decisions. However, this is not always the case. To assess the efficacy of treatment options for chronic conditions such as T2DM, decision makers must often rely on techniques that indirectly compare existing data or on Bayesian analysis, an approach that predicts patient outcomes when clinical trials are not feasible. Pharmacoeconomic analyses are also reliant on techniques such as Markov modeling to compare the cost-effectiveness of new and existing therapies because direct evidence is often not available. As the cost of diabetes care continues to rise, it is imperative that decision makers have the ability to effectively predict the relative utility of various treatment options. The use of CER can facilitate this process.

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