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REVIEW ARTICLE

HEALTH ■ CLINICAL ■ POLICY

Using Indirect Evidence to Determine the Comparative Effectiveness of Prescription Drugs: Do Benefits Outweigh Risks?

Huseyin Naci, MHS[a], Rachael Fleurence, PhD[b]

[a]LSE Health, Department of Social Policy, London School of Economics and Political Science, London, UK; and [b]Oxford Outcomes, Bethesda, MD

ABSTRACT

Health care decision-makers rarely have the appropriate evidence to evaluate the comparative clinical effectiveness of new and existing prescription drugs. In the absence of head-to-head trials comparing all available drugs, indirect comparisons of randomized trials can offer a valuable approach to investigators evaluating the comparative effect of multiple drugs. Indirect comparisons, particularly methods that allow the combination of direct and indirect evidence obtained from randomized trials, can assist in identifying which of multiple prescription drugs works better than others. In this article, we discuss the benefits and risks of using indirect evidence and make the case in favor of its wider use within the comparative effectiveness research efforts in the US. We further argue that the use of indirect comparisons should be pursued in cases where trials comparing the interventions of interest are available.

KEYWORDS: Comparative effectiveness research; Indirect comparison; Mixed treatment comparison; Network meta-analysis; Prescription drug therapy

Interest in the conduct and synthesis of research to compare different health care interventions is gaining momentum. After the American Recovery and Reinvestment Act of 2009 allocated $1.1 billion to support comparative effectiveness research (CER) in the US, the Patient Protection and Affordable Care Act of 2010 provided sustained federal funding through 2019.[1] The promise of CER in the US is to provide information to help patients, consumers, clinicians, and payers make more informed clinical and health policy decisions. Evidence on the comparative clinical effectiveness of multiple interventions will, in theory, allow patients, providers, and policymakers to distinguish between health care interventions in terms of their relative therapeutic value in routine clinical practice. An important aspect of CER is determining the relative clinical effectiveness of similar prescription drugs.

Evidence on the comparative clinical value of similar drugs currently marketed in the US is generally not available. The Food and Drug Administration does not require active-comparator trials for market authorization, and drug labels do not include statements about a drug's comparative effect: approval of a new drug may imply to

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prescribers that newer drugs represent an advance over older ones.[2-4] In the absence of head-to-head studies comparing all similar drugs, prescribers do not have adequate evidence to evaluate the comparative clinical value of new and existing drugs. Consequently, they are often unsure about a drug's appropriate place in practice.

For addressing comparative effectiveness questions, generating adequate evidence on the relative clinical effectiveness of drugs will depend on having the appropriate research methodologies. The randomized controlled trial is often considered the gold standard of whether a drug works or is better than another. Unfortunately, randomized trials are often costly and take a long time to complete. Although observational studies may offer an alternative to randomized trials, they may be prone to bias. Nevertheless, observational studies have advantages as they may offer a closer reflection of real world practice and availability of a wide range of data sources and outcomes. In some cases, they are also less resource intensive than randomized trials.[5]

Investigators therefore need to weigh the relative value of waiting for evidence from future randomized or observational studies or making decisions based on the existing evidence base. It is surely not practical — or feasible — to invest vast sums of comparative effectiveness research dollars to generate evidence from future studies to determine the comparative effectiveness of all existing *and* new drugs. An efficient strategy then is to initially prioritize the review and synthesis of the existing body of evidence.

Evidence review methods such as meta-analyses, which are statistical tools for pooling the results of several comparable studies, are increasingly used to summarize available evidence. In the absence of head-to-head comparisons that compare drugs with each other *within* studies, researchers have extended established meta-analytic approaches to also conduct indirect comparisons of multiple drugs *between* studies. In this context, indirect evidence refers to the type of evidence obtained from comparisons of interventions using data from separate studies, in contrast to direct evidence obtained from an individual study (Figure 1).

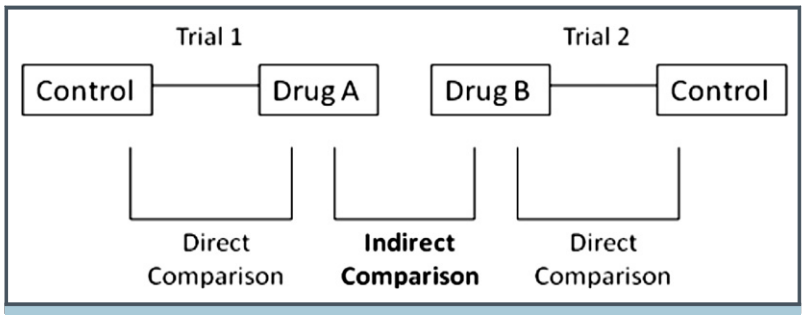

FIGURE 1: Indirect comparison of Drug A vs Drug B.

In this article, we discuss the benefits and risks of using indirect comparisons and make the case in favor of their wider—and yet careful—use within the comparative effectiveness research efforts in the US. We argue that indirect comparisons, particularly methods that allow for the inclusion of both direct evidence and indirect evidence, can assist in identifying which of multiple prescription drugs works better than others. While we recognize the benefits as well as limitations of reviews of observational studies in informing CER questions, in this article we review the indirect comparison methodology that builds upon randomized trial evidence alone.

AN ENTANGLED BODY OF EVIDENCE

Systematic reviews and meta-analyses, when assembling comparative effectiveness evidence, play a central role by summarizing the existing evidence base and informing health care decision-making based on current information. As the level of interest in evidence-based medicine has grown, there has been a proliferation of systematic reviews and meta-analyses. The estimated number of systematic reviews published in the peer-reviewed literature increased exponentially over the past decade, with over 3500 systematic reviews published in 2009 alone. Many of these are multiple reviews of competing treatments for a single clinical