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Commentary

Methodologies for Pharmaceutical Effectiveness and Pharmacoeconomics Research

Recently, the Office of Technology Assessment (OTA) issued a report entitled *Identifying Health Technologies That Work: Searching for Evidence* (1) that promoted the use of randomized clinical trials (RCTs) and large simplified trials (LSTs) for effectiveness research and pharmacoeconomics while criticizing the use of observational studies in automated claims databases due to the inherent biases in nonexperimental research. The exclusive use of RCTs to establish efficacy should not necessarily preclude the use of other research designs for analyses beyond efficacy such as economic and effectiveness research. Other research designs such as meta-analyses of RCTs, epidemiological or observational studies, including retrospective cohort and case-control studies, as well as modeling, or a combination of these approaches, are important methodologies to consider for pharmacoeconomics and effectiveness in the "real world" due to their ability to provide large patient populations in an efficient manner.

Although RCTs can assess the occurrence of common adverse events (AEs), the rare or delayed AEs must be identified using epidemiological or observational research, i.e., postmarketing surveillance in large populations. Prospective RCTs have serious limitations for pharmacoeconomics, in addition to their expense and small sample size due to their lack of applicability to a "real world" setting. The exclusion and inclusion criteria for RCTs lead to a self-selected population of compliant providers and patients with good internal validity, but questionable external validity. In contrast, observational studies in medical claims databases provide actual treatment experience of patients in a "real world" setting.

The OTA Report (1) proposed enhanced use of RCTs, specifically, LSTs because comparisons of treatment efficacy and adverse events require especially, large sample sizes. LSTs are RCTs conducted in thousands of patients using simplified protocols with data collection on only a few critical outcomes such as mortality and based on a committed infrastructure of the community health care provider (2). Pharmacoeconomic studies in clinical trials with protocols requiring collection of resource use both at regularly scheduled clinic trial site visits and at unscheduled visits to physicians offices, hospitals, and emergency rooms in between clinic trial site visits may be imparting a complexity inconsistent with LSTs. Moreover, even in LSTs, differences between comparison therapies need to be large; otherwise the results are ambiguous, e.g., relative effectiveness of tissue-type plasminogen activator (TPA) and streptokinase (3, 4). Although LSTs are less expensive than traditional RCTs on a per patient basis and provide a larger patient pool, they require considerable resources due to their large sample size. However, these trials can be justified if they significantly improve treatment practice guidelines.

Contrasted to RCTs and LSTs, retrospective observational studies in large, automated claims databases present an efficient and inexpensive method of patient analyses for pharmacoeconomics. As the costs of computer assembly, retrieval, and analyses are progressively reduced, such automated database studies can become indispensable to the field of pharmacoeconomics. Types of studies that have been conducted in automated claims databases include natural history of disease, i.e., patients' characteristics, current therapies and associated health care resource use and costs for a particular indication; comparative effectiveness of therapies, i.e., effectiveness research and pharmacoeconomics; drug utilization review; post marketing surveillance for rare adverse events; and disease state management. Moreover, these databases can provide health care resource use data associated with alternative therapies for economic modeling, and in some novel applications can provide a sampling frame for clinical trials especially for a rare disease, as well as document the resource use during unscheduled visits of patients in clinical trials by the chronological medical history in automated claims. Retrospective observational studies fill the voids presented by RCTs, as a more efficient and inexpensive alternative to LSTs.

The OTA Report (1) cited three examples of observational studies that were in fact confirmed in randomized clinical trials including studies in tonsillectomy (5), coronary artery bypass surgery (6), and use of beta-blockers after heart attack (7). Yet, the OTA Report (1) dismissed observational study results showing mortality benefits from prophylactic administration of lidocaine in myocardial infarction patients in conflict with clinical trials results (8), even when the clinical trials did not have the power to detect these small mortality differences. The OTA Report (1) continues that multiple observational studies in databases with similar results do not necessarily raise confidence levels because of their underlying biases. The primary limitation of these databases are the potential underlying biases affecting comparability in the treatment groups due to nonrandom selection of patients. These potential limitations include selection bias, i.e., physician treatment selection based on risk status; information bias, i.e., inaccuracies in the measurement of exposure, disease or confounder status; comparison bias, i.e., inappropriate reference group; and confounders, e.g. risk factors, severity of illness (9–12). In observational studies, researchers use statistical techniques such as stratification and multivariate analyses to detect and control confounding and biases in nonrandom samples (13, 14). These techniques are predicated on the availability of these confounding variables either in the automated databases or through review of medical records. However, findings across disparate studies with different biases due to variations in patient populations, study designs, selection criteria,

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and risk factors will be consistent if the biases are small compared to the magnitude of the findings. Thus, raising confidence in the validity of these results.

Since no study design is perfect for every research question, there is a legitimate place for all types of prospective, retrospective, and modeling studies depending on the research issues, resources, and time frame necessary to make responsible policy decisions. Moreover, encouraging the recording of risk factors, clinical data, health behaviors, and drugs in inpatient setting, as well as having medical records available for verification would enhance the breath and depth of the observational databases for pharmaceutical effectiveness and pharmacoeconomics research (15).

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