BRIEF WORKSHOP REPORT

Seeking the Balance between Harm and Benefit: The Role of Pharmacosurveillance in Choosing the Drugs We Should Take

Trouver l'équilibre entre les torts et les bénéfices : le rôle de la pharmacosurveillance dans le choix des médicaments qu'il convient de prendre

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Pharmacosurveillance is the regular monitoring of medications in real clinical practice for benefits and harms. This paper outlines the advancements of the Manitoba Centre for Health Policy (MCHP) and others to date in participating in pharmacosurveillance research. It proffers what we could do in the future to produce information that informs the balance between benefit and harm of the use of pharmaceuticals.

A research framework for looking at questions of pharmacosurveillance was posed at the beginning of this workshop (Metge et al. 2005a). According to Health Canada, safety, efficacy (whether a drug works) and quality are the attributes of a drug that are evaluated when its

manufacturer is seeking a licence for its use in Canada (Metge et al. 2005b). Drawing a parallel with Donabedian's structure/process/outcome quality paradigm (Donabedian 1982), Dr. Metge outlined the work that MCHP has done regarding the attributes of quality:

- Utilization of quantitative data on the access, extent, variability and cost of the use of pharmaceuticals corresponds to Donabedian's focus on structure.
- Appropriateness, or determination of whether the right drug was prescribed to the right person at the right time and in the right dose, aligns with assessment of process.
- Outcome, or the net of benefit and harm when a pharmaceutical is prescribed, dispensed and taken under real-life circumstances, is similar to Donabedian's third step in the model of quality.

At MCHP, several studies have developed methods to look at these attributes of quality. Early work concentrated on "quantifiability" and in developing the Drug Programs Information Network (DPIN) database for research purposes, which included linking to other data sets (e.g., physician visits, hospitalizations, vital statistics). DPIN data include persons' use of pharmaceuticals from birth to death for most of the population.[1]

Several government initiatives and individual researchers have taken advantage of the DPIN's linkages. For example, from a drug utilization perspective we know that elderly residents of Manitoba, on average, cost more per year than other Manitoba residents, yet the amount paid per dose differs significantly (Metge et al. 2005a). Elderly persons' (65+ years) total costs for pharmaceuticals are more per year than persons less than 65 years.

We have also found, by applying an appropriateness lens, that physicians appear not to be using a "step-up"[2] approach to prescribing for new, uncomplicated hypertensive patients. When doctors were given a choice of entities for the first prescription to newly diagnosed persons with hypertension, 64% of these prescriptions specified the top-end, or most expensive, option (Metge et al. 2003).

A study of utilization and costs of antipsychotic agents in Manitoba was undertaken using data housed at MCHP, and showcased by Dr. Silvia Alessi-Severini. The time series perspective of this study provides an overview of what has changed in the use of antipsychotic agents in Manitoba over time (Alessi-Severini et al. 2008). For example, second-generation antipsychotic agents (SGAs) rapidly overtook first-generation agents (FGAs) in 2001. Over a 10-year span (1996–2006), the market share of FGAs fell from 90% to 20%, while SGAs' market share rose from 10% to 80%.

Costs per dose of SGAs are far greater than costs of FGAs. A recent master's thesis completed at the University of Manitoba (Vasilyeva 2009) considered the difference in adverse events in the elderly population treated with both FGAs and SGAs. SGAs were significantly associated with a lower risk of all-cause mortality but a significantly higher risk of myocardial infarction compared to FGAs. No significant difference was found between the two kinds of agents for cerebrovascular events, cardiac arrhythmia and congestive heart failure. The entire data source for these findings was the MCHP Repository (years 2000–2007).[3]

Dr. Ingrid Sketris discussed two examples of the use of administrative data in the area of pharmacosurveillance, one of them involving Manitoba data. Case 1 compared antibiotic use in three Canadian provinces – Nova Scotia, Saskatchewan and Manitoba (Sketris et al. 2004). A rich panel of other data (patient, provider and system factors; industry marketing strategies) offered explanations for the findings that the use of antimicrobials differed markedly among the three provinces. No appropriateness analysis was done; however, the finding that the use of different agents was very different among the three provinces was interesting. Pharmacosurveillance data (on appropriateness) was not largely considered as the purpose of the study was to see if comparative studies of drug utilization across provinces was possible (Health Transition Funding from the late 1990s).

Case 2 looked at the effectiveness of disease-modifying drugs (DMDs) in delaying the progression of multiple sclerosis. This project has built on the use of registries, examining the development of policies on prescription drug coverage based on evidence culled from research (Brown et al. 2007). Specifically, by combining clinical registry data and administrative data, Nova Scotia has been able to estimate the treatment effect size of DMDs in the context of real-world clinical practice (Fisk et al. 2005). These estimates were similar to the efficacy estimates from the pivotal licensing trials.

The implications for Manitoba are that the synthesis of administrative and clinical data can be powerful in answering questions about both safety and effectiveness. Nova Scotia has a MS registry; Manitoba has a bone mineral density (BMD) registry, and similar studies have used Manitoba Health and other clinical data. Pivotal licensing trials are the clinical trials required for a pharmaceutical company to receive its licence to market the drug in Canada. The value added from the Nova Scotia study was the importance of obtaining permission to link administrative data with clinical data and the increased knowledge that can be gained from doing so.

At the conclusion of the formal presentations, questions were posed to the participants for discussion. These focused on the knowledge translation aspect of pharmacosurveillance research. For example: "We may have done a good job at providing knowledge support to decisions about the effectiveness of prescription drugs and their use, but do we perceive that the knowledge has been used?" "Will the evolution of the Drug Safety and Effectiveness Network (CIHR/Health Canada) help us to improve the translation of pharmacosurveillance knowledge?"

Discussion of these points concluded that the answer to the first question was most likely no, for now – many decision-makers appear to continue to question the validity of the observational data used to report on drug safety and effectiveness (Metge et al. 2005b). Discussion of the second question was inconclusive, since the new Drug Safety and Effectiveness Network was just beginning the process of being established. However, several participants expressed hope that because DSEN has been given sufficient funding and a sufficiently strong mandate that it will help the evidence produced by it to be used in informing both individual and population-based decisions about the use of pharmaceuticals.

NOTE

[1] DPIN data do not include drugs dispensed through First Nations Inuit Health nursing stations and some federal programs (prisons and the RCMP). Less than 5% of data were missing, although for nursing stations in at least

one northern region, upwards of 20% of data may have been missing. A recent analysis of this missing data has not been done.

[2] The act of applying (or prescribing) the minimum pharmacological force necessary to achieve a stated therapeutic objective when initiating therapy.

[3] The master's thesis had not been completed when this session was offered.

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