

RESEARCH, EDUCATION, AND THE IMPACT OF PRESCRIPTION

COMPLIANCE ON BETTER MEDICINE

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The environment for healthcare, biomedical research, and health professional education is changing rapidly. There is, however, no doubt that enlightened drug policy, with appropriate inputs from research and education, is likely to remain a critical element in the achievement of “better medicine”. Drug utilization data from Canada and several other jurisdictions indicate that the overall use of both prescription and non-prescription drugs continues to increase rapidly, ⁽¹⁾ consuming a steadily growing proportion of the total healthcare expenditure. Appropriate decision-making in drug therapy and the achievement of “value for money” in prescribing is critical to optimal care in both publicly and privately funded healthcare systems.⁽²⁾ Clinical decision makers are also under pressure from several quarters to use more drug therapies and to employ newer and usually more expensive treatments.⁽²⁾ However, over the past 15 years, there has been an increased emphasis placed on evidence-based decision making in therapeutics with recognition that choices should be based on the highest possible levels of evidence, in particular, data obtained from randomized clinical trials. Ironically, at a time when reliance on such evidence has become general in Canada, new imperatives have emerged for increasingly individualized therapy that recognizes extreme variability in drug response influenced by both genetic and environmental factors.⁽³⁾ It is now understood that the standardized recommendations for drug therapy reflected in clinical guidelines based on randomized controlled trials are not likely to be appropriate for all patients under all circumstances.

Decisions about drug therapy are increasingly based on considerations of relative safety among competing treatments; however, most evidence which can be brought to bear on this element in choice comes from observational studies. It is rare that a prescriber has the benefit that would accrue from early availability of safety data from randomized controlled trials. Most important information about safe prescription choices comes from real world experience after a drug is marketed.^(4,5)

Health Care Decision-making

The power spectrum of decision-making in healthcare has shifted radically over recent years. Major hospitals and medical specialists and sub-specialists have sacrificed some of their hegemony and an increasingly prominent role has been taken by patients, consumers generally, and their families as well as by government and private sector payors.

The prospect for a new 21st century health care system was described by the Institute of Medicine 2001 in their report entitled "Crossing the Quality Chasm".⁽⁶⁾ The new "simple rules" that may define the future health landscape are shown in Table 1.

At the same time, the architecture of supporting biomedical research has also altered. The previous isolation of basic molecular research from clinical and population research has been broken down. Biomedical research is increasingly perceived as a continuum with great emphasis being placed on the overlap between cellular and molecular research as reflected in our growing knowledge of genomics and proteomics, clinical investigation, and population health sciences. Most importantly, many health professional educational institutions and tertiary care hospitals have now focused their research activities on knowledge transfer and integrative biologic research. This type of translational study includes the assessment of care gaps and the active study of corrective interventions.

A National Drug Research Agenda

The rapidly changing environment for healthcare, biomedical research, and education has also influenced the pursuit of optimal drug therapy. There has been widespread recognition of the need for a national research agenda that would support decision making in drug therapy and that would include several elements critical to choice among competing therapeutic agents.

- Basic pharmacology and toxicology
- Clinical studies of drug action
- Comparative clinical trials
- Studies of patient safety and safe medication practices
- Analyses of system errors capable of leading to drug misadventure
- Therapeutic outcomes research
- Pharmaco-economic studies

There are many impediments to the achievement of a national research agenda supporting drug therapy. Chief among these is the lack of independent research funding to support clinical drug investigations. A full clinical trial program is extremely costly and government agencies, including CIHR, have generally avoided the funding of large trials, even when the results may be critically important to policy decisions in a particular therapeutic field. In addition, Canada lacks adequate human resources to engage in more than occasional large-scale clinical trial efforts. The shortfall in trained resources is compounded by the fact that academic institutions have traditionally discounted clinical research and population-based disciplines such as epidemiology and behavioural sciences that are important to clinical trial activity. The result has been a rather uneven capability in clinical investigation across Canada. The most successful centres currently are heavily reliant on sponsorship by the pharmaceutical industry.

There is a particular need for greater effort devoted to the establishment of relative safety for medications. In spite of the obvious clinical importance of such capacity, the needed methods for risk identification, risk analysis, and study of risk management techniques are emerging only slowly in academic centres. With increasing knowledge of the human genome, it is apparent that the assessment of drug safety will require greatly expanded understanding of pharmacogenetic mechanisms influencing drug action. Safety cannot be adequately assessed on the basis of randomized controlled trials as presently conducted. An additional area of concern is safe medication practice which itself requires direct study if we are to avoid systematic errors that remain largely hidden but are likely responsible for thousands of drug misadventures and deaths in Canada annually.⁽⁷⁾

Educational Agenda and Priorities

Educational strategies have a great deal to contribute to the overall improvement of drug therapy and achievement of better therapeutic outcomes.

The educational agenda should include a broad-based educational strategy which would underpin a comprehensive approach targeting optimal drug therapy. The educational strategy should range from efforts to improve teaching about life sciences in elementary and secondary schools to the development of enhanced programs for professional and post-professional training for healthcare givers. Overall, the greatest improvements in drug therapy are likely to be made through expansion of the public's health literacy and enhancement of the individual ability to demand appropriate therapies.

Priorities in education should include capitalizing on new information technology, improving the dissemination of research data as a support of therapeutic decision-making, teaching new methods for analysis and communication of risk, and improving the professional preparation of doctors, nurses and pharmacists to promote appropriate therapeutic decisions. Web-based drug information will also play a key future role in raising the public's health literacy level.

Canadian Resources in Research and Education for Drug Management

Canada has excellent institutional supports for better drug management in medical faculties, pharmacy faculties, nursing faculties, and teaching hospitals. There are, in addition, outstanding programmatic resources (figure 1) in clinical pharmacology which is well represented in at least 9 Canadian medical schools, clinical toxicology and drug safety which is established in 5 universities, pharmacoepidemiology units operating in 11 universities and pharmaco-economic/outcomes research services presently represented in at least 7 universities. Academic study of drug policies and the application of information technology to improved clinical care is also developing rapidly.

While this represents considerable infrastructure, there are still few granting programs directly targeting improved drug therapy although some funds are available from the Canadian Institutes for Health Research, the Health Services Research Foundation, the Canadian Coordinating Office for Health Technology Assessment and from provincial Ministries of Health.

What Have Others Done that We Should Emulate?

Overall, Canada has been slow to provide financial support for education and research activities devoted to the pursuit of better drug therapy. Because responsibility for therapeutic drug insurance, to the extent that it currently exists in Canada, rests at a provincial level there has been some support for evaluation activities from provincial governments. In British Columbia, the Therapeutics Initiative has been concerned with drug evaluations and the Centre for Health Services and Policy Research has addressed broader issues. The Manitoba Centre for Applied Health Research has gathered pharmacoepidemiologic data. In Ontario, the Centre for Evaluation of Medicines at McMaster University and the Institute for Clinical Evaluative Sciences at the University of Toronto have both studied drug therapy, prescribing patterns and pharmaceutical outcomes. Similar roles have been played in Quebec by the Centre Hospitalier Université de Montréal (CHUM) and the Epidemiology Department at McGill University. At Dalhousie University, the Nova Scotia government and CIHR have supported a Population Health Research Program shared by the Faculties of

Medicine and Pharmacy with interests in pharmacoepidemiology, prescribing practice and health outcomes.

On a national level, there has been little formal support for drug evaluation activities although enthusiasm has waxed and waned for such activity in proportion to the degree of enthusiasm at any given time for a national formulary or national pharmacare. Approximately 10 years ago, the federal government was the leading proponent of a national pharmaceutical strategy which would have led to the creation of a Canadian Agency for Pharmaceutical Information (CAPIA). More recently, Health Canada has supported calls for the creation of a National Pharmaceutical Drug Use Information System (NPDUIS), and a National Institute for Patient Safety. The federal, provincial, and territorial ministers of health are also committed to the development of a common drug review system which will, of necessity, require expanded drug evaluation capacity.⁽⁸⁾

More substantial government sponsored drug evaluation can be found internationally, where examples include the European Medicines Evaluation Agency (EMA) and the National Institute for Clinical Excellence (NICE) in the United Kingdom. In the United States, the Agency for Healthcare Research and Quality (AHRQ) created a network of twelve evidence-based practice centres 5 years ago and has more recently supported Centres for Education and Research in Therapeutics (CERTs) in 7 universities. The Food & Drug Administration supports an Office for Drug Surveillance.

The Agency for Healthcare Research and Quality resides in the American Department of Health and Human Services. It has a mandate to support research designed to improve the quality of healthcare, reduce its costs, improve patient safety, reduce medical errors, and broaden access to essential services. Improvement of drug therapy has been a major focus of AHRQ and 2 years ago, a network of 7 centres for education and research in therapeutics was created to foster a collaborative approach among governments, manufacturers, caregivers, consumers, academic organizations, insurance companies and research organizations. The 7 CERTs reported almost 100 active research projects in 2001.⁽⁹⁾

Compliance with Prescription Drug Orders

Non-compliance, or as it is sometimes called, non-adherence, can take several forms:

- Taking more than the dose prescribed
- Taking less than the dose prescribed or none at all
- Altering timing or interval between doses
- Taking medications under contraindicated conditions

The extent of non-compliance varies with disease severity, patient socio-economic status, disease treatment choice, and duration of therapy. Most surveys of compliance suggest that overall, 20% of prescriptions are never filled and it is estimated that 50% of those prescriptions that are filled are taken incorrectly. Non-adherence rates appear to be particularly high in vulnerable populations such as the frail elderly or among patients with depression or psychosis.

In 1976, Dr. David Sackett of McMaster University suggested that there were no less than 250 factors that had been identified as contributing to the problem of non-adherence or non-compliance.⁽¹⁰⁾ Dr. Sackett's colleague, Dr. Brian Haynes at McMaster suggested in 1979 that "at a minimum we must aspire to improve adherence only with those treatments or actions for which we have reasonable evidence for efficacy and we must maintain constant vigilance for any harmful result of our interventions."⁽¹¹⁾

Consequences of Non-Compliance

The literature suggests that non-adherence with medication regimes accounts for considerable cardiovascular morbidity and mortality, such as stroke following poorly controlled hypertension. In psychosis, 40% of relapse is estimated to be attributable to non-adherence. Perhaps most importantly, resources committed to drug therapy are wasted if a disease state requires consistent chronic therapy but is treated only sporadically or not at all because of non-compliance. This problem has been reported particularly in relation to the widespread use of cholesterol lowering drugs for the treatment of hyperlipidemia. It can be estimated in Canada that the indirect cost of non-compliance is in the range of several billion dollars annually. However, since non-compliance is so widespread, if it were possible to correct the problem instantaneously the immediate result would be a probable 50% overall increase in Canadian drug expenditure. Before a major campaign against non-adherence/non-compliance is mounted, convincing evidence should be required of benefit likely to result from such major expenditure.

Compliance Improving Strategies

Peck and King reported in 1982 that there are only 6 strategies that have been proven to provide good results in compliance improvement.⁽¹²⁾ These include:

- Written instructions to the patient
- Delivery of drugs in special packaging
- Description of tailored or simplified regimens
- Involvement of the patient in therapeutic planning
- Engagement of the patient with self-monitoring
- Provision of incentives for reinforcement purposes

As well, mixed but generally positive results have been described as resulting from improved communication between physicians and patients, education programs, and the offering of warnings to patients about the consequences of non-adherence. All other compliance-improving strategies that have been tested have produced negative or equivocal results.

While it is generally agreed that compliance can be improved through the interventions suggested by Peck and King, rigorous cost-effectiveness analysis of compliance-improving strategies has not generally been conducted and there is some justifiable skepticism about the therapeutic improvements that might result from such expenditure. Even those most enthusiastic about the benefits of drug therapy may concede that some patients may well be making a correct decision to avoid their prescribed therapies.

Critical Public Policy Choices

It seems clear that a heightened effort in research and education, and the improvement of prescription compliance should yield better therapeutic outcomes. It is less clear how this can be achieved within Canada's healthcare system. The renewed interest in a national pharmacare program may provide an opportunity for selective policy choices to bring about overall improvement in prescribing choice and therapeutic outcomes.

If a national drug insurance program is to be created in Canada, there will be a requirement for a research and education infrastructure sufficient to support national standards based on appropriate research including the following:

- Descriptive research that clarifies the burden of illness and defines treatment needs.
- Causal research, including pharmacogenomics, to predict benefits and risks of treatment.
- Interventional research consisting of independently funded clinical trials conducted to the fullest extent possible.
- Applied evaluative research, including pharmacoepidemiologic surveillance, risk assessment, and studies of safe medication practice.

The research and education infrastructure needed to support a national drug insurance program should ideally be independent of both drug regulators and manufacturers although remaining responsive to their needs. The role of drug payors in funding such a system will remain open to debate; however, ideally, all stakeholders, including consumers, should be expected to contribute to the infrastructure costs of the needed initiative.

Conclusion

There are several possible public policy choices that warrant careful consideration as part of an informed debate on the merits of a national pharmacare system. The choices shown in figure 2 could prove equally important to the success of initiatives already undertaken by Health Canada and the Federal, Provincial, and Territorial Ministries of Health with respect to a common drug review, improved patient safety and institution of a national drug use information system.^(7,8) Research and education capacities are likely to remain critical to Canadian efforts at attaining the best possible drug therapy outcomes for available resources.