The value of independent drug assessment

Type 2 diabetes in British Columbia as a case study to explain the work of UBC's Therapeutics Initiative.

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The November 2018 issue of the *BCMJ* included two articles about diabetes management in British Columbia and a guest editorial that referred to the Therapeutics Initiative (TI). We would like to respond to the information provided in that issue by clarifying our organization's goals and processes and our role in BC's health care system.

The TI was established in 1994 by the Department of Pharmacology and Therapeutics in cooperation with the Department of Family Practice at the University of British Columbia. We are an independent academic unit, separate from government and the pharmaceutical industry, funded by a grant to UBC from the BC Ministry of Health.

Our mission is to provide physicians and pharmacists with up-to-date, evidence-based, practical information on prescription drug therapy. A founding principle and raison d'être was health professionals' need for independent, unconflicted assessments of new drug therapies to balance drug industry–sponsored information sources. Over the last 25 years, our team has developed expertise in identifying and critically appraising both published and unpublished sources of evidence. Taking the time and effort to apply these skills meticulously to the review of clinical trial evidence distinguishes our approach from many other groups.

In his guest editorial,[1] Dr Ehud Ur states that the TI "provides physicians with its own unique interpretation of the diabetes literature through bimonthly Therapeutics Letters that often cast doubt on the findings of robust trials and guideline recommendations issued by highly respected international organizations." Our interpretation of evidence from clinical trials is not, indeed, unique. We consider the work of regulatory agencies such as the US FDA and European Medicines Agency, other independent drug bulletins, and other academic groups. Our analyses are often relatively concordant with those published by nonconflicted experts in diabetes.[2-4] Our uncertainty about how to interpret the EMPA-REG OUTCOME trial, seen by some as relatively controversial, was reflected in the narrow 12:11 approval of its cardiovascular prevention indication by the FDA's advisory committee and shared by an independent assessment from Spain.[5,6]

The article by Dr Maureen Clement and colleagues,[7] and Dr Ur's editorial note differences between some recommendations from Diabetes Canada, the BC Guidelines and Protocols Advisory Committee, and certain conclusions drawn by the TI

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from our evidence reviews. Dr Clement and colleagues note that "general practitioners and specialists looking for guidance in the complex pharmacological management of type 2 diabetes in BC can find themselves frustrated by contradictory recommendations from these three bodies: Diabetes Canada, the British Columbia Guidelines and Protocols Advisory Committee, and the Therapeutics Initiative."

It should not be surprising if health care professionals and people with type 2 diabetes are confused or frustrated by the range of guidelines available, and their mutability over time. This problem is hardly unique to diabetes care. Over the life of the TI (and long before) there are numerous examples of guideline recommendations that were subsequently repudiated or superseded by objective evidence from clinical trials. This applies to nephrology, cardiology, infectious diseases, intensive care, pediatrics, many fields of surgery, and various types of screening and other preventive interventions.

Different organizations composed of specialists, patient advocates, or government officials have varying mandates and apply markedly different processes to assess evidence. This can yield a broad spectrum of recommendations, many of which will not look wise in retrospect. Were only the vagaries of human biology so simple to understand and control as some direct-to-consumer TV ads make it look: "I just love my numbers!"

The role of the TI is not to write guidelines for any disease. Our mandate is solely to assess randomized clinical trial evidence and to summarize our detailed assessments for clinicians to help them and their patients make evidence-informed drug therapy decisions.

We employ a standardized, systematic, transparent process to all drug assessments, including those for glucose-lowering medications. If our results differ from recommendations offered by pharmaceutical manufacturers and industry-funded thought leaders, it is likely because our review process differs in a number of ways. We start by defining the outcomes of greatest importance to patients, ranked in a standard hierarchy derived from Cochrane Collaboration methodology. Our reviews routinely attempt to include unpublished data available now from regulatory reviews and from the detailed clinical study reports compiled by clinical trial sponsors, and from trial registry websites. Including regulatory documents and clinical study reports (when available) is critical, rather than superfluous, to informing conclusions regarding a new drug or indication. This often involves very hard work. For example, the version of the LEADER trial of liraglutide for type 2 diabetes in the *NEJM* comprises 12 pages plus a 69-page appendix. The corollary US FDA briefing document is 166 pages. The transcript of the FDA advisory committee meeting is 382 pages, and the underlying clinical study report for LEADER is 3603 pages. It is not clear that Diabetes Canada's Expert Committee has included this level of review to inform its most recent pharmacotherapy recommendations.[8]

Focusing on clinical outcomes that are most relevant for patients accounts for many differences in interpretation of clinical trials. For example, Dr Clement and colleagues write that "Glycemic control is an important risk factor for microvascular disease, including retinopathy, nephropathy, and peripheral neuropathy. Early improved glucose control slows progression to these endpoints." Yet considering the same clinical trial evidence, the 2018 American College of Physicians Guidance Statement on HbA1c targets for type 2 diabetes articulates more clearly that "the main effect of more intensive glycemic control is a small absolute reduction in risk for microvascular surrogate events, such as retinopathy detected on ophthalmologic screening or nephropathy defined by development or progression or albuminuria."[3] Similarly, the 2017 meta-analysis cited by Dr Clement and colleagues did not identify an effect of intensive glucose control on the risk of neuropathy, and noted that effects on retinopathy and nephropathy were modest and determined by less-serious complications.[9]

A founding policy of the TI in 1994 was to ensure that members of our academic group have no conflicts of interest with manufacturers of pharmaceuticals. This is neither because of antagonism to the important benefits of innovative pharmacotherapies nor to the challenges of developing them. It is because we agree with those who have concluded that conflicts may introduce insidious biases with the potential to impair scientific judgment. It has been clear for years that conclusions and recommendations of clinical guidelines could be strengthened greatly through attention to contemporary standards that increase their trustworthiness. The 2011 report of the US National Academies, "Clinical Practice Guidelines We Can Trust,"[10] explores in depth how guidelines should be developed and what standards should be employed to ensure their reliability, including a foundation of transparency and management of conflicts of interest. Its approach has been followed in some recent guidelines developed in the US and Canada, yet such high standards remain an exception rather than the rule in medicine.

If BC clinicians feel confused by guidelines that offer conflicting advice, the best remedy would be for complex scientific research to be analyzed free from pharmaceutical industry funding, and then crafted into trustworthy recommendations that are relevant to individual patient care. As others have pointed out, this is a

more than Herculean endeavor; most clinical trials screen out the type of complex multimorbidity seen by doctors in everyday practice.[11]

We think that our careful and unconflicted scrutiny of research findings helps to produce succinct Therapeutics Letters that physicians can trust as a resource to serve their patients. However, we have never claimed to have all the answers or recommended treatment paradigms for individual patients. To suggest that the TI is responsible for confusing and frustrating BC's family physicians and specialists underrates their intelligence, education, and judgment. We believe BC doctors are capable of thinking critically for themselves and synthesizing information from different sources. This is especially so when they can access unbiased and rigorous evidence about drug therapies, based on thorough and systematic reviews. Understanding the strengths and weaknesses of evidence about drugs for type 2 diabetes (or any other condition), combined with clinical experience and willingness to integrate their patients' goals, provides the best foundation for optimal care. This is really the definition of evidence-based medicine: "the conscientious, explicit and judicious use of current best evidence in making decisions about the care of individual patients."[12]

BCMJ readers may also wish to understand better the process used by the Pharmaceutical Services Division of the Ministry of Health to decide on drug coverage. This is explained in detail at www2.gov.bc.ca/gov/content/health/health-drug-coverage/pharmacare-for-bc-residents/what-we-cover/drug-coverage/drug-review-process-results.

After Health Canada approves a drug for use in humans, the national Common Drug Review (CDR) of the Canadian Agency for Drugs and Technologies in Health reviews drug submissions from drug manufacturers for potential public plan coverage. Most of the submissions are then reviewed by the ministry's Drug Benefit Council (DBC) to contextualize CDR's evidence syntheses and recommendations. Sometimes the ministry requests additional analysis from the TI. Our members may attend DBC meetings when requested to explain evidence and answer questions. However, TI members neither vote on nor make funding decisions. We help to elucidate and clarify available evidence, typically from randomized controlled trials. The Pharmaceutical Services Division then makes its funding decisions after considering the recommendations of the CDR and DBC.

Over the past 25 years the TI has enjoyed international recognition for our consistently rigorous approach. We have often been among the first to understand the real available evidence about drugs, and it is hardly surprising that this has frequently proven controversial. If additional evidence changes our understanding of the merits of new diabetes drugs, we will naturally welcome therapeutic approaches that are more successful than the limited tools available to doctors and patients since the discovery of insulin.

We welcome challenges to our interpretation of evidence and would be pleased to work with our critics to exchange ideas regarding literature review methods. As always, we look forward to hearing from BC doctors, including those who are critical of our approaches or conclusions.

Competing interests

Drs Wright, Bassett, Perry, and Tejani receive part-time salaries from UBC via the Ministry of Health Contributory Agreement (grant) to UBC to support TI.

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