

## Challenges to Evidence-Based Prescribing in Clinical Practice

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Evidence-based medicine (EBM) can be defined as the integration of best research evidence with clinical expertise and patient values.<sup>1</sup> The recent transition from authority-based medicine to EBM has driven fundamental changes in clinical practice, health research, and medical education. This transition has generally been applauded, although its implementation has been difficult and sometimes harmful.<sup>2</sup> Major challenges facing evidence-based prescribing may be organized into 3 categories: (1) the availability of relevant evidence, (2) the time and ability to interpret evidence appropriately, and (3) the translation of knowledge into clinical practice. Using statin prescribing patterns as a case example, we discuss each of these 3 categories.

### The Case Example: Statins

Several statins with similar safety profiles are currently available, providing clinicians with a variety of treatment options for reducing low-density lipoprotein cholesterol (LDL-C) levels. The case described here examines the impact of the introduction of new statins on clinician prescribing behavior among patients receiving long-term therapy with older members of the drug class.

We conducted a population-based cross-sectional time series analysis using administrative healthcare databases that cover more than 1.4 million residents of Ontario, Toronto, Canada, aged at least 66 years. These patients have universal access to prescription drug coverage, hospital care, diagnostics, laboratory tests, and physician services. This study was approved by the Ethics Review

Although there appears to be widespread support of evidence-based medicine as a basis for rational prescribing, the challenges to it are significant and often justified. A multitude of factors other than evidence drive clinical decision-making, including patient preferences and social circumstances, presence of disease–drug and drug–drug interactions, clinical experience, competing demands from more pressing clinical conditions, marketing and promotional activity, and system-level drug policies.

**KEY WORDS:** clinical practice, evidence-based prescribing, pharmacy practice.

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The linked databases included computerized pharmacy records of the Ontario Drug Benefit Program, which records prescription drugs dispensed to all Ontario residents 65 years of age and older and contains prescription-related information such as date of dispensing, drug strength, quantity dispensed, and intended duration of therapy. An overall error rate of less than 1% in this drug database has been reported.<sup>3</sup>

The study's timeframe was divided into 45 quarterly intervals from the first quarter in 1994 (1994Q1) to the first quarter in 2005 (2005Q1). At the beginning of each quarter, we identified long-term users of 2 relatively older statins—simvastatin and pravastatin. We defined long-term statin users as individuals who used the same statin for at least 3 consecutive 120-day intervals. Two relatively newer statins—atorvastatin and rosuvastatin—were included in the Ontario provincial formulary in August 1997 and September 2003, respectively. For both simvastatin and pravastatin, our main outcome measure was the percentage of long-term users who switched statin therapy as defined by the new dispensing of a statin other than the one used for 3 consecutive 120-day intervals. We also ex-

amined the most recent dose of the older statin prior to the switch to determine whether switched users were taking the maximum dose of simvastatin or pravastatin prior to switching. Time series analysis,<sup>4</sup> an approach for modeling autocorrelation in temporally sequenced data, was used to evaluate changes over time.

## Challenges of Evidence-Based Prescribing

### AVAILABILITY OF RELEVANT EVIDENCE

Although there has been a considerable increase in clinical research activity recently, optimal evidence is often not available for many clinical decisions. Ideally, clinicians require well-designed, large-scale clinical studies that assess patients reflective of common clinical practice who are being treated with the drug of interest and all clinically relevant comparators, with sufficient follow-up to allow for the assessment of clinically meaningful patient outcomes.

In our case example, such trials existed for both pravastatin<sup>5</sup> and simvastatin<sup>6</sup> that demonstrated significant reductions in clinically meaningful outcomes such as myocardial infarction and death from coronary heart disease. These trials were published well before the introduction of atorvastatin and rosuvastatin. In contrast, a considerably smaller trial examining a surrogate endpoint, changes in levels of LDL-C, was published 7 months after the availability of atorvastatin on the public formulary in Ontario.<sup>7</sup> This trial suggested that atorvastatin was more potent than other statins in reducing LDL-C levels. Although LDL-C levels are correlated with atherogenesis, such a surrogate endpoint is not a replacement for more clinically meaningful outcomes, as evidenced by recent ezetimibe/simvastatin data suggesting possible cardiovascular harm despite greater LDL-C level reduction relative to simvastatin alone.<sup>8</sup> Indeed, recent evidence suggests that pravastatin, simvastatin, and atorvastatin may not differ significantly with respect to long-term clinical outcomes.<sup>9</sup> Similar data assessing surrogate endpoints in small trials accompanied the addition of rosuvastatin to the public formulary.

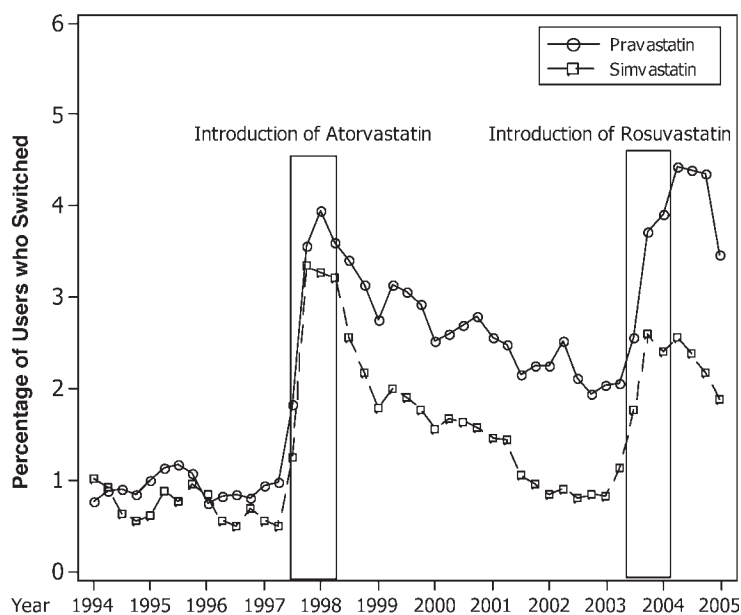
Despite the availability of ideal information for pravastatin and simvastatin, there were significant increases in the proportions of patients switching from these established drugs to atorvastatin and rosuvastatin upon their release ( $p < 0.01$  for both drugs; Figure 1). In the case of atorvastatin, switching from either pravastatin or simvastatin to atorvastatin increased significantly even prior to the publication of the CURVES study.<sup>7</sup> One possible explanation is that some clinicians, particularly those who, by nature, are early adopters, may believe that evi-

dence on surrogate endpoints that have some level of correlation to clinical outcomes may be sufficient to change practice. The limitations of this analysis include lack of information on the reason for switching and LDL-C levels, lack of direct measure of adherence or appropriateness of use, the inability to track drug samples, and the potential presence of other factors that may have been related to the switching.

### TIME AND ABILITY TO INTERPRET EVIDENCE APPROPRIATELY

The lack of time and training on the part of the well-intentioned clinician to critically and independently evaluate evidence threatens the very basis of EBM. Volumes of research are published daily, leaving many clinicians complaining of information overload and insufficient time and technical training to read and interpret the available evidence,<sup>10</sup> which is crucial in distinguishing between poor- and high-quality evidence and interpreting information when studies of equally high quality conflict in their findings. Consequently, many clinicians rely heavily on information from pharmaceutical industry representatives and marketing and promotional information. The quality of information from these sources and its impact on clinical practice have been criticized, given the potential conflict of interest; for instance, the number of visits with pharmaceutical representatives has been negatively correlated with quality of prescribing.<sup>11</sup>

In our case example, significant promotional activity at the time of product launch may have fueled the significant increases in switching rates from older statins to newer



**Figure 1.** Quarterly percentage of long-term users of simvastatin and pravastatin who switched statins.

ones despite the lack of any compelling evidence to prompt such prescribing behavior.

#### TRANSLATION OF KNOWLEDGE INTO CLINICAL PRACTICE

Assuming the availability of information, time, and ability to independently and critically evaluate available evidence, translation of information from evidence to practice may still be challenging. The majority of published clinical research is in the form of clinical trials or observational studies, both of which have their own advantages and limitations. Data from clinical trials are typically very narrowly focused on specific patient populations often not reflective of the majority of patients who would normally be seen in clinical practice and adhere to atypically strict monitoring parameters. Such practices are often in place to maximize patient safety and trial efficiency. Consequently, translating information from the often artificial environment of a clinical trial to clinical practice can be problematic; a drug therapy shown to be highly beneficial in a clinical trial was recently associated with population harm when adopted into clinical practice.<sup>2</sup> Observational studies are typically plagued with biases that are often difficult to interpret and sufficiently address and typically lack the level of clinical detail to answer many relevant clinical questions. The widespread adoption into clinical practice of hormone replacement therapy for cardiovascular prevention in postmenopausal women was based largely on observational studies that were unable to sufficiently capture clinical differences between patients who were using and those who were not using hormone replacement therapy and were unable to separate any temporal patterns in utilization (ie, there may be a long-term benefit but a short-term harm associated with hormone replacement therapy).<sup>12</sup> Seemingly beneficial cardiovascular effects of hormone replacement therapy were then challenged by well-designed clinical trials that demonstrated cardiovascular harm in the short term.

It would also be naïve to assume that evidence is the only factor in clinical decision-making. A multitude of other factors influence it, including patient preferences and social circumstances, presence of disease–drug and drug–drug interactions, clinical experience, competing demands from more pressing clinical conditions, marketing and promotional activity, and system-level drug policies.

In our case example, despite suggestions from national evidence-based guidelines to titrate a statin to its maximal dose prior to switching to another statin,<sup>13</sup> the majority of patients switching from either pravastatin or simvastatin to atorvastatin or rosuvastatin were not taking maximal doses of the older statins; for example, more than 70% of patients taking pravastatin and more than 80% of patients taking simvastatin were receiving less than 40 mg/day prior to switching to atorvastatin. However, the rationale behind the observed increase in switching rates is un-

known—studies of administrative databases often do not contain such information—and many possible explanations for this behavior can be theorized. For example, the observed increase may have been driven in part by physician and patient early adopters to new technologies (eg, patients demanding the new therapy once it was available based on patient-directed promotional activity),<sup>14</sup> adverse events that were tolerated by the patient until a new therapeutic option became available, or physician reluctance to increase the dose of the older statin due to expected adverse events. Although every effort should be made to include evidence in the clinical decision-making process, clinicians must rely on clinical experience, common sense, and a sound understanding of the principles of clinical pharmacology while making decisions in the best interest of patients and their preferences.<sup>15</sup>

#### Conclusions

Although there appears to be widespread support of EBM as a basis for rational prescribing, the challenges are significant and often justified. These include the lack of relevant clinical information, the time and ability of busy clinicians to review and interpret the available evidence, and the translation of knowledge into clinical practice. Reductive linear reasoning that assumes that findings from clinical studies can be uniformly applied to the majority of patients in routine practice is often faulty and potentially harmful. In providing the best possible care to patients, it must be remembered that knowledge translation is, in itself, complex and relies on a myriad of factors in clinical decision-making, of which evidence is just one.

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### Desafíos de la Prescripción Basada en la Evidencia en la Práctica Clínica

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#### EXTRACTO

A pesar de que parece existir un amplio soporte de la medicina basada en la evidencia como base para la racionalización de la prescripción, los desafíos para ello son significativos y, a menudo, justificados. Existen multitud de factores diferentes a la evidencia que dirigen la decisión clínica, incluyendo las preferencias del paciente y los condicionantes sociales, la existencia de interacciones entre enfermedad y medicamento y entre medicamentos, la experiencia clínica, los condicionantes que suponen la existencia de otras condiciones clínicas más importantes, las actividades de marketing y promocionales, y el nivel de implantación de políticas farmacéuticas del sistema. Este trabajo revisa los desafíos asociados con la prescripción basada en la evidencia utilizando como ejemplo el cambio de conducta de estatinas durante la introducción de una nueva estatina

Traducido por Corinne Zara Yahni

### Défis Relatifs à la Prescription Fondée sur les Preuves en Pratique

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#### RÉSUMÉ

Bien que le principe de prescription basée sur les preuves bénéficie d'un large consensus au sein de la communauté, il soulève également des défis majeurs et souvent justifiés. Une multitude de facteurs autres que les preuves existe et influence la prise de décision telle les préférences du patient, les circonstances sociales, l'interaction maladie-médicament ou médicament-médicament, l'expérience clinique, les demandes venant de conditions cliniques fréquentes, les activités promotionnelles et de mise en marché, et les politiques de soins de santé. Ce manuscrit révisé les défis associés à la prescription basée sur les preuves et utilise comme exemple la substitution d'une statine pour une autre lors de l'introduction de nouvelles statines sur le marché.

Traduit par Marc M Perreault