The Value of Case Reports

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In this issue of the *Canadian Journal of Hospital Pharmacy* (*CJHP*), we publish 2 unique papers, a case report on propofol-induced green breast milk, by Rainone and others,[1] and a case series on patients receiving ticagrelor and acetylsalicylic acid after placement of a Pipeline embolization device for cerebral aneurysm, by DeGrote and others.[2] Given that case reports and case series are found at the lower level of the "evidence hierarchy", one might question why the *CJHP* places value in publishing them.

Despite their subservience to randomized controlled trials in the evidence hierarchy, well-written case reports and case series play an important role in evidence generation and in clinical practice.[3] Case reports are categorized as patient-oriented research reports, which, by definition, include a description of some novel aspect related to a disease or therapy in one or more patient cases. In the absence of other evidence, case reports may thus provide valuable information to clinicians.[3]

Case reports may help with investigating new drug-related side effects, as does the report by Rainone and others[1] in this issue. A published case report may stimulate other clinicians to report similar cases, which may in turn prompt further investigations to more systematically evaluate a new hypothesis. By generating new hypotheses, case reports may also assist with the discovery of new diseases, therapeutic approaches, or indications for existing treatments. For certain special populations, case reports may initially constitute all of the available evidence, until postmarketing surveillance is conducted after completion of clinical trials or until larger observational cohorts are available, as for the case series described by DeGrote and others[2] in the setting of embolization procedures for cerebral aneurysm.

Case reports may also help us to understand how results from randomized clinical trials of typically healthier patients, with fewer comorbidities, translate to more diverse populations in real-world clinical practice. When we extrapolate research evidence beyond a clinical trial population, which often happens in our daily practice, unexpected results may occur. Case reports may be useful to help identify limitations in our extrapolations and raise awareness of potentially adverse consequences. They may also highlight the practical challenges of applying evidence to practice and may help to bridge the gap between evidence and practice, as did the case report on rivaroxaban use in a morbidly obese patient, previously published in this Journal.[4]

Who better than clinicians—who are the first to see how new therapies are being used and how patients respond to the new therapies—to share their valuable insights and experience in the medical literature through the use of case reports? Adverse reactions to new drugs may not be recognized until the postmarketing surveillance period, and it may be years before trends start appearing in the literature. It is vital for clinicians to contribute to the literature through case reports so that we can gain practical insights into the process of translating evidence to the real-world setting. Given that case reports can stimulate further research, we can acknowledge their contribution to the evidence base. Many professional organizations that develop guidelines, such as the American Heart Association, give case reports a lower ranking (e.g., level C evidence category), similar to that of clinical opinion. However, an objectively written, well-structured case report may actually constitute stronger evidence than subjective opinion.

Case reports may also provide an entry point into medical writing for junior clinicians. Therefore, it is important to also understand their limitations. By their nature, case reports have a small sample size, do not allow for blinding of participants and clinicians, and, because of their retrospective design, may be

missing relevant data that were not evaluated or documented in the medical record. Case reports cannot be used to infer causality or to calculate incidence or prevalence (because of lack of a denominator) and, most importantly, they have the potential to allow over- or mis-interpretation when the case is generalized to clinical practice.

A well-written case report should demonstrate critical thinking and logical reasoning, provide mechanistic insights, and tell a clear and compelling patient story. Many journals offer general information for authors on preparing case reports (including *CJHP*; see https://www.cjhp-online.ca/pages/files/AuthorInstructions.pdf), and some have published articles explaining how to write case reports. However, one study found that more than half of the 1316 emergency medicine case reports evaluated failed to provide essential information that would have increased transparency and replication, necessary attributes for research reports.[5] Given the inadequate quality of many published case reports, the CARE guidelines (which are similar to the CONSORT guidelines for reporting randomized controlled trials) have been developed to provide recommendations to standardize the publication of case reports.[6]

The CARE guidelines are based on a 13-item checklist for reporting cases, including a valuable visual timeline; they even encourage adding a patient perspective, where suitable.[6] The CARE guidelines are not specific for reporting cases of adverse drug reactions, nor do they recommend the inclusion of a causation algorithm (some journal-specific author guidelines for case reports do refer to causation algorithms). Although the Naranjo probability scale,[7] the most commonly used causation algorithm, represents an improvement over simple clinical judgment, its subjective nature limits its performance, and some questions have been raised about its reliability and validity.[8] No universally accepted method for assessing the causation of adverse drug reactions currently exists, and research is underway to develop new algorithms to assess the probability of adverse drug reactions, particularly in specialized settings.[9]

In recent years, publishing case reports has become a big business, with more than 150 journals now focusing on this area. A recent review showed that many of these are open-access journals with high acceptance rates, with about half having potentially questionable or predatory practices that raised concern among the investigators.[10] For a case report to become a valuable addition to the literature, it should be well written and published in a reputable, peer-reviewed journal. Therefore, authors considering publishing case reports must use due diligence in selecting the appropriate journal for their submission.

A fundamental tenet of evidence-based clinical practice is to use the best available clinical evidence, and at times, a case report or case series is the best available evidence to guide decision-making.[3] *CJHP* values case reports that contribute to the clinical evidence base and that may stimulate further investigations. Therefore, the Journal's editors welcome submission of high-quality case reports, which may represent important contributions to the literature.

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