Motherisk and *Canadian Family Physician*

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I beseech you, in the bowels of Christ, think it possible you may be mistaken.

Oliver Cromwell

In 2015 the guidelines for the management of nausea and vomiting in pregnancy (NVP) developed by Motherisk and endorsed and published by the Society of Obstetricians and Gynaecologists of Canada,[1] recommendations from which were published previously in the pages of *Canadian Family Physician* (*CFP*),[2,3] came under critical scrutiny.[4,5]

These guidelines have consistently endorsed the use of the combination of doxylamine-pyridoxine as the first-line therapy for NVP. A recent systematic re-evaluation of the evidence by Persaud and colleagues revealed that the combination of doxylamine-pyridoxine is not superior in efficacy to pyridoxine alone.[4]

The re-analysis by Persaud et al of a 1997 meta-analysis conducted by Motherisk,[6] which purported to show that women treated for NVP with the combination medication had a lower risk of fetal malformations, revealed the original analysis to be flawed and its conclusions wrong.[4] Furthermore, the study by Persaud et al suggests that while large cohort studies have found no association between doxylamine-pyridoxine and malformations, some smaller studies show an increased risk of pyloric stenosis and some childhood malignancies,[5] although the overall risk of these remains small.

What does this information mean for family physicians and their pregnant patients? What do relationships with organizations like Motherisk mean for generalist family medicine journals like *CFP* in light of the flawed evidence supporting their recommendations, which were published in this journal?

Not supported by best evidence

The first question is relatively straightforward to answer. We agree with the conclusions of Persaud and his colleagues that there is not, at this time, clear evidence that the combination of doxylamine-pyridoxine is more effective in the management of NVP than pyridoxine alone and that the grade IA evidence recommendation in the Motherisk guidelines published in *CFP* and by the Society of Obstetricians and Gynaecologists of Canada is not supported by the current best evidence.[5] Although in July 2016 Health Canada published a review of the safety of doxylamine-pyridoxine and concluded that its benefits continue to outweigh its risks when used as authorized,[7] family physicians treating NVP could consider pyridoxine alone as first-line therapy. This recommendation is consistent with clinical practice guidelines from the United States[8] and Australia.[9] Family physicians could also consider following the recommendations from the National Institute for Health and Care Excellence[10] or the Royal College of Obstetricians and Gynaecologists[11] in the United Kingdom, which recommend antihistamines alone.

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Reflection on a long-standing relationship

The answer to the second question is more complex and deserves close scrutiny.

The relationship between *CFP* and Motherisk dates back 2 decades. No written record of the beginning of this relationship exists, but it is almost certain that, at the time, Canadian family physicians were looking for the best available evidence about the safety of prescription and nonprescription drugs for their pregnant patients. Motherisk was then perceived as a highly reputable organization dedicated to answering just such questions, and *CFP* thought it appropriate to help facilitate Canadian family physicians' access to that information.

Over the past year or so the reputation of the Motherisk organization has been called into question as a result of concerns about the potential influence of Duchesnay, the manufacturer of Diclectin, the combination of doxylamine-pyridoxine, on the Motherisk NVP guidelines.[12]

Canadian Family Physician ended its long-standing relationship with Motherisk at the end of 2015. In part this was because of the concerns about the independence of the organization from industry raised by the work of Dr Persaud and his colleagues. The editorial staff and the Editorial Advisory Board of the journal reflected deeply on the issues raised by its long-standing relationship with Motherisk. Several lessons have been learned, which we wanted to share with our readers.

Influence and integrity

It is impossible to know to what extent the recommendations for the management of NVP in the guidelines were directly influenced by Motherisk's relationship with a pharmaceutical company, but there is widespread influence of industry on the creation of clinical practice guidelines in medicine.[13] Furthermore, reputable advocacy organizations like Motherisk might be especially attractive and susceptible targets for such influence.

It is important for us to recognize that *CFP* added to the validity of the NVP guidelines by reinforcing the credibility of Motherisk, allowing it a privileged place in the journal. Unlike most other manuscripts submitted to *CFP*, Motherisk articles were not subjected to a full double-blind peer-review process. This was based on assumptions about the quality of the work and the integrity of the organization. This approach was allowed to persist over the intervening years until the more recent concerns arose.

Evidence is not static

As generalists, family physicians will continue to use clinical practice guidelines, most of which are currently developed by non–family physician specialists or disease-specific organizations. In doing so we must take the best available evidence as we know it and apply it in our practices, but be constantly aware that we might be wrong or that the evidence might be flawed.

Would a more formal double-blind peer-review process have detected the problems with the Motherisk NVP guidelines? It is hard to know with certainty. It was only through a thorough re-evaluation of the literature, prompted by questions from a patient to a family physician researcher, that led to this discovery. Evidence is not static; re-evaluation of accepted truths should not be seen as a weakness as new information comes forward.

Canadian Family Physician will likely continue to have ongoing relationships with different organizations or institutions if these best serve the information needs of family physicians and their patients. However, this episode is a clear lesson that we must do so with greater scrutiny, with more formal agreements, and only with those that do not have any ties to industry or other entities that would create, or even appear to create, information or guidelines that have a purpose other than clear and science-based benefit to patients in our care.

Science and journals such as *CFP* that publish science in service to good care are not static entities. They are human endeavours dedicated to discovery and application of knowledge and have the imperfections that all human endeavours will demonstrate from time to time. It is vitally important to learn from those imperfections rather than deny they exist. We began with a quote from history underscoring the need for humility in all things. We close with words put in the mouth of Galileo by Bertolt Brecht in his eponymous play:

> *The aim of science is not to open the door to infinite wisdom, but to set a limit to infinite error.*
>
> Bertolt Brecht, *Life of Galileo*

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Competing interests
None declared

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