

with patients' clinical condition, and measurements are best completed while patients are on gluten-containing diets.

—Aliya Khan, MD, FRCPC, FACP
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by e-mail

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Chest pain, dyspnea, and cough

How benign is benign use of nitrofurantoin for prophylaxis of urinary tract infections (UTIs)? I have read with great interest an article by L. Nicolle and colleagues, "Uncomplicated urinary tract infection in women. Current practice and the effect of antibiotic resistance on empiric treatment."¹ The authors refer to the efficacy and safety profile of nitrofurantoin for short-term treatment of uncomplicated urinary tract infection. It is important to mention, however, that long-term treatment with nitrofurantoin can have dangerous complications.

Recently, I have seen several elderly women in the emergency department who were receiving prophylactic nitrofurantoin for recurrent UTIs. These patients have been prescribed nitrofurantoin for years, despite known warnings and adverse side effects that are well described in the nitrofurantoin monograph in the *Compendium of Pharmaceuticals and Specialties*.

Use of nitrofurantoin for longer than 6 months can lead to subacute, acute, or chronic pulmonary hypersensitivity reaction, the 2 most common forms of which are interstitial pneumonitis and pulmonary fibrosis. Patients might present with dyspnea on exertion, cough, chest pain, and malaise. Risk of lung toxicity varies among patients receiving prophylactic nitrofurantoin. A 10-year retrospective Swedish study of long-term nitrofurantoin use has demonstrated that older women are more prone to developing lung toxicity than their male counterparts or younger women.²

The potential irreversible side effects that are well described in the literature are not commonly considered when assessing patients in the emergency department who are receiving nitrofurantoin prophylaxis. A recent small study looked at the radiologic changes in elderly women receiving nitrofurantoin prophylaxis who presented with dyspnea, cough, and chest pain. Authors of the study concluded that the radiologic findings are relatively nonspecific on chest film and usually include bilateral areas of ground-glass opacities on computed tomography of the chest.³

There are several medications, chemicals, and bacteria—such as bleomycin, methotrexate, cyclophosphamide, amiodarone, procainamide, penicillamine, gold, asbestos, silica, mycobacteria, and fungi—that are well known to the medical community for their potential to induce pulmonary toxicity. However, health care providers, and especially trainees, are not well educated about potential risks related to nitrofurantoin-induced lung toxicity.

In the last decade, many immunologic mediators were shown to play a role in drug-induced lung fibrosis, such as interleukin-1, interleukin-13, tumour necrosis factor-alpha, and interferon gamma in bleomycin-induced pulmonary fibrosis.⁴ Nitrofurantoin induces pulmonary hypersensitivity reactions, likely via redox cycling of the nitro group and its radical anion; this process is also known as oxidative stress.⁵ Several medications have been shown to ameliorate drug-induced lung toxicity in animal models.⁴ No antidote has been found in human beings, however.⁵

No randomized controlled trials have examined potential treatment strategies for nitrofurantoin-induced pulmonary inflammatory reactions. The standard clinical approach is to discontinue an offending agent and determine whether the patient requires in-hospital monitoring and supportive care. Some reports refer to steroid therapy in acute and chronic cases as being beneficial for resolution of symptoms. Fortunately, most nitrofurantoin-induced lung toxicity is reversible when the medication is discontinued.

It is very important to consider these side effects when prescribing nitrofurantoin for prophylaxis and when assessing patients who have dyspnea, chest pain, and cough and who are receiving long-term therapy with nitrofurantoin.

—Val E. Ginzburg, MSC, MD
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by e-mail

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Clarifying omega-3 fatty acid recommendations

I applaud Dr Schwalfenberg's review of omega-3 fatty acids, published in the June 2006 issue of *Canadian*

Family Physician.¹ A recent article published in the *British Medical Journal*,² however, which found no decrease in mortality or cardiovascular disease with omega-3 supplementation, appears to contradict Dr Schwalfenberg's conclusions. I and others are left wondering. Comments would be appreciated.

—Andy Biro, MD, MSC, CCFP
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by e-mail

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Thank you for the great article on omega-3 fatty acids in *Canadian Family Physician*.¹ But a recent article in *Patient Care*,² which cited study findings that men who consumed the most alpha-linolenic acid were twice as likely to be diagnosed with advanced prostate cancer as those who consumed the least alpha-linolenic acid, was worrisome. Do you have any comments or more information regarding omega-3 (or alpha-linolenic acid) and prostate cancer?

—Nelson Daniels, MD
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by mail

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Response

First, I would like to thank Dr Biro for his valid question.

The *British Medical Journal* (BMJ) meta-analysis by Hooper et al¹ came to the conclusion that there is a null effect for omega-3 fatty acid supplementation. However,

was it not only 2 years ago that another article in the *BMJ* said the opposite?²

More than 30 responses by prominent researchers have shown their concern with the recent *BMJ* article. One reviewer, Ka He, from Northwestern University, lists at least 5 reasons this review is inadequate.¹ A second reviewer stated that the DART-2 trial included in the *BMJ* meta-analysis has a number of methodologic problems and should not have been included¹ (inclusion of this trial alone made the results come out quite differently). Another reviewer stated that the *BMJ* article was a "dis-service to public health."¹

Dietary recommendations and exercise are first-line therapy for cardiovascular disease. As physicians we instruct our patients to avoid certain "bad fats" (saturated and trans fats) and cholesterol. What about providing instruction on good fats? One of the reasons I wrote my article³ was to present dietary guidelines on good fats in cardiovascular disease.

Omega-3 and omega-6 are essential fatty acids and must be supplied to us by diet. Omega-3 fatty acids have well-known biologic effects, which I listed in Table 1 in my article (this table includes only the cardiovascular effects; there are many others).³ These are ignored in the review by Hooper et al.¹

An outstanding systematic review (which included 97 studies and 275 000 patients) on various lipid-lowering agents and diets has concluded that omega-3 fatty acids are more effective than statins in reducing overall mortality and cardiac mortality.⁴

Most of the studies used in the *BMJ* review do not address the omega-6-to-omega-3 ratio. There is evidence that a 4:1 ratio is required for maximum benefit for cardiovascular disease and less than 2:1 to have any effect on cancer. This is almost impossible to achieve with our diet today (Canadian guidelines are currently 6:1). An excellent book, *Omega-6/Omega-3 Essential Fatty Acid Ratio: The Scientific Evidence*, reviews this.⁵

Confounders in the *BMJ* meta-analysis include the influence of the omega-6-to-omega-3 ratio; the pre-existing omega-3 status in the participants (if you