Prostate-specific antigen screening

I read Dr Robert Burn's letter on prostate-specific antigen screening[1] with personal interest, having recently been declared "cured" [of prostate cancer] 6 years after brachytherapy (radioactive iodine) treatment.

Given that my father had incidental prostate cancer later in his life, and considering myself to be at some increased risk, I enrolled in the multicentre SELECT (Selenium and Vitamin E Cancer Prevention Trial) study some 10 years ago. The purpose of the study was to test, in a double-blinded trial, the hypothesis that selenium or vitamin E might decrease the incidence of prostate cancer. (The study was abandoned when it was found that the incidence of type 2 diabetes increased with one of the drugs and the incidence of prostate cancer slightly increased with the other. Incidentally, on inquiry I discovered that I was in the double-placebo group.)

I further reasoned that if I did have the disease, being part of a study would result in fast-tracking to treatment. This proved to be the case when a modest increase in prostate-specific antigen screening tests year to year (although still less than 4) led to a biopsy and the discovery that I had the disease in both lobes. What to do? I was offered, of course, the full range of treatment options and considered myself to be a "poster boy" for brachytherapy, which seemed to me the best choice, with good outcomes and fewer side effects. On subsequent inquiry, I was informed by a study nurse that more than 100 cases had been picked up in the study (of more than 1100 participants) and that I was the only one who had opted for brachytherapy.

I must confess that the idea of "sitting on a touch of cancer" had little appeal to me as an option. My procedure was uneventful and "went very well," in the words of my radiotherapist who performed the procedure. Side effects have been of the nuisance variety, with no performance issues, at least for a few years. (I now use Viagra for enhancement purposes, likely age-related I tell myself—I'm 73.)

Having been declared cured and now back in the care of my family physician for routine follow-up, I often wonder if I am among those thought by some to have been overtreated for minimal disease. We'll never know. But I am pleased with the course of action I took and to call myself a survivor.

—John Biehn MD CCFP FCFP
London, Ont

Competing interests
None declared

Reference
1. Burn R. The tragic trajectory [Letters]. *Can Fam Physician* 2011;57:655-7.

Difficult balance being gatekeepers

I read Dr Burns' letter, "The tragic trajectory,"[1] published in the June issue of *Canadian Family Physician* with interest. It is difficult to keep the balance and not allow the tail to wag the dog. Who has more medical experience and knowledge between patient and physician? It takes courage to draw the line—and to hold the line—at the best evidence. It is not necessary to do a test because the patient insists, especially when he or she only has emotional reasons to request it and especially when the patient's unique circumstances scream to us that the requested test or intervention is not indicated!

—John L. de Couto MD
Burnaby, BC

Competing interests
None declared

Reference
1. Burn R. The tragic trajectory [Letters]. *Can Fam Physician* 2011;57:655-7.

Women with depression should be offered folic acid

We disagree with Nahas and Sheikh's conclusion that there is insufficient evidence to recommend folate for major depressive disorder (MDD).[1] Our review of the same studies cited in their review of alternative medicines for depression leads us to the opposite conclusion and reveals misinterpretations of the data. We outline these studies here so that readers can draw their own conclusions.

In a 10-week randomized, blinded trial, Coppen and Bailey measured the effect of folate when combined with fluoxetine for the treatment of major depression (N=127).[2] The relatively unimpressive average improvement, noted by Nahas and Sheikh, is shown to be the result of a sex-specific response variable. Based on intention to treat and per protocol analyses, response and remission rates as well as end-point depression scores in the folate plus fluoxetine group were shown to be clinically superior for women but not men (**Table 1**).[2] Only around 3 to 4 women need to be treated with folic acid for 1 to achieve treatment response or remission. This highly clinically meaningful result has also been overlooked in recent depression guidelines.[3,4] It

Table 1. Randomized trial results of adjunctive folate treatment in major depressive disorder: *A 10-week trial measuring the effect of folate when combined with fluoxetine.*

	MEAN HDRS AT END OF STUDY*		RESPONSE RATE,*† %		REMISSION RATE,*† %	
TREATMENT	MEN (N = 40)	WOMEN (N = 69)	MEN (N = 40)	WOMEN (N = 69)	MEN (N = 40)	WOMEN (N = 69)
Folate	12.3	6.8	61.1	93.9	50	72.7
Placebo	10.5	11.7	63.6	61.1	50	47.2
Difference	+1.8	-4.9	-2.5	+32.8	0	25.5
P value	NS	<.001	NS	<.005	NS	<.06

HDRS—Hamilton Depression Rating Scale, NS—not significant.
*Per protocol analysis comparing fluoxetine and folate with fluoxetine alone (intention-to-treat subanalysis not provided); study dropout rate was 14%.
†Response: > 50% reduction in HDRS; remission: HDRS final score ≤ 9.
Data from Coppen and Bailey.[2]

is worth noting that mean folate levels were low but within the normal range at baseline in the study and, as such, response was not linked to overt folate deficiency.

Nahas and Sheikh also cited an earlier 52-week randomized blinded trial by Coppen et al that measured the effect of folate augmentation of "affectively very well" lithium clinic patients with unipolar depression (n = 53), bipolar disorder (n = 17), and schizoaffective disorder (n = 5).[5] The investigators indicated that the affective morbidity of study participants was so low that it was difficult to assess the value of any additional therapy. In the unipolar depression group, the Beck Depression Inventory (BDI) average score at baseline was approximately 8, indicating minimal symptoms. Therefore, this trial was not designed to assess the antidepressant effect of folate in MDD. Nonetheless, a significant improvement in BDI was observed in the unipolar depression folate group ($P < .02$) but not the placebo group (**Table 2**). Unfortunately, a subgroup analysis based on sex was not reported. These data are not consistent with Nahas and Sheikh's conclusion of no difference in BDI scores between groups.

Table 2. Randomized trial results of adjunctive folate treatment in major depressive disorder: *A 52-week trial measuring the effect of folate augmentation in lithium clinic patients with unipolar depression.*

TREATMENT	MEAN BDI AT START OF STUDY (N = 53)	BDI AT END OF STUDY (N = 53)	*P* VALUE
Folate	7.4	6.3	<.02*
Placebo	8.7	9.2	NS*

BDI—Beck Depression Inventory, NS—not significant.
*Baseline to end point within group comparison (between group comparison not provided).
Data from Coppen et al.[5]

The third cited trial enrolled only people with folate deficiency (red-cell folate <200 µg/L) who met the diagnostic criteria for depression (n = 24) or schizophrenia (n = 17).[6] There were no enrolment criteria based on depression severity and no baseline depression data were provided. A hint that depression severity was minor at

baseline were the 1-month Hamilton Depression Rating Scale scores of less than 10 in both groups. For these reasons, the trial is not applicable to address the question of folate augmentation for the routine patient with MDD starting a course of antidepressants. Moreover, a sex-specific subanalysis was not reported.

Finally, Nahas and Sheikh refer to but discount Passeri and colleagues' randomized comparison of folate versus trazodone added to standard psychotropic medication for the treatment of depression in cognitively impaired patients.[7] We believe that the absence of a placebo group prevents any conclusion from being formed regarding the effectiveness of either agent in depressed elderly patients with mild to moderate dementia.

Based on the Coppen and Bailey randomized trial[2] (the only trial to test adjunctive folate in clinically depressed patients), folate provides a clinically meaningful benefit to women initiating standard antidepressant medication when used in a typical supplementary dose of 0.5 µg daily. The muted benefit found in other trials might represent the average of nonresponders (men) and responders (women) with MDD as well as their low burden of depressive symptoms. Folate's use is made more attractive by its safety profile, low cost, and potential for providing other benefits. The use of folate in sexually active women of childbearing age might add the further benefit of protecting against neural tube defects to the fetus if pregnancy occurs. With baseline folate measures being unnecessary, not recommending folate to this group of women is difficult to justify. In contrast to Nahas and Sheikh, we believe the evidence to date supports its routine use in clinical practice in women with depression and we encourage depression guideline developers to reconsider its place in therapy.

—Jonathan Melong
—David Gardner PharmD MSc
Halifax, NS

Competing interests
None declared

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