the adverse reactions. However, about 35% of patients overall did not complete the trials.

To determine if rates of adverse reactions were higher in clinical practice than in the literature, we undertook an independent study to examine adverse events associated with Zyban for smoking cessation in rural family practice. The study was carried out in Peace River, Alta. (population 6500) during the period April 2001 to February 2002. Patients 18 years of age or older who received a first-time prescription of Zyban for smoking cessation were enrolled and followed prospectively for 2 months. Previous Zyban users, those who were using Wellbutrin (another brand of bupropion) and those with an underlying seizure disorder were excluded from the study.

We enrolled a total of 39 patients, of whom 15 (38%) discontinued Zyban because of adverse reactions. The most common reasons for discontinuation were neuropsychiatric symptoms (tremors, agitation or confusion), insomnia and rash. An additional 7 patients (18%) decreased the dosage from twice daily to once daily because of adverse reactions. In total, 32 (82%) of the patients reported at least one adverse reaction (including neuropsychiatric symptoms reported by 16, insomnia by 12, dry mouth by 9 and rash by 7). Nine patients (23%) required additional medical care (a total of 10 visits), and one patient (3%) was admitted to hospital. Eleven (28%) of the patients quit smoking, and we are currently determining if those who quit continue to be nonsmokers.

Because of the small sample size, the generalizability of our findings is unknown. However, they indicate that rates of discontinuation because of adverse effects may exceed those previously reported.[2,3] Therefore, larger, independent, community-based studies are needed. It has been postulated that less than 10% of all adverse events are reported.[1] To improve this rate, physicians need to be more diligent in reporting adverse reactions to the Canadian Adverse Drug Reaction Monitoring Programme. Only then can we obtain a true estimate of adverse reaction rates for medications commonly prescribed in Canada.

Michael Kolber
Assistant Clinical Professor
G. Richard Spooner
Professor and Chair
Olga Szafran
Research Coordinator
Department of Family Medicine
University of Alberta
Edmonton, Alta.

References

1. Mintzes B, Bassett K, Wright JM. Drug safety without borders: concerns about buproprion [letter]. *CMAJ* 2002;167(5):447.
2. Hurt RD, Sachs DP, Glover ED, Offord KP, Johnston JA, Dale JC, et al. A comparison of sustained-release buproprion and placebo for smoking cessation. *N Engl J Med* 1997;337(17): 1195-202.
3. Jorenby DE, Leischow SJ, Nides MA, Rennard SI, Johnston JA, Hughes AR, et al. A controlled trial of sustained-release buproprion, a nicotine patch, or both for smoking cessation. *N Engl J* Med 1999;340(9):685-91.

Competing interests: None declared.

Acknowledgement: This study was funded by the Alberta Rural Physician Action Plan.

Graves' disease in children

Jody Ginsberg's clinical review[1] is appropriate for physicians treating adults with Graves' disease, but children with this condition may not present in the same way as adults, and the diagnosis and management of the disorder differ in several respects between adults and children.

The clinical findings in children can be similar to those in adults, often involving multiple systems in a subtle manner. Most affected children do have diffuse goitre and ocular signs, but neither is a common, isolated presenting complaint.[2] Rather, children often present with behavioural disturbances such as decreased attention span, difficulty concentrating (which leads to poorer academic performance), hyperactivity, difficulty sleeping, tachycardia, tremor and weight loss despite increased appetite.[3]

As in adults, hyperthyroidism in youth can be confirmed by measurements of serum thyroid-stimulating hormone, free thyroxine and triiodothyronine. However, a 24-hour radioiodine uptake scan is not needed to elucidate the cause of hyperthyroidism in young patients because, although other diagnostic possibilities exist, hyperthyroidism in this age group is almost always (more than 95% of cases) related to Graves' disease.[4]

The recommendation to consult a specialist to assist in managing Graves' disease is mandatory for both adults and children. However, although the treatment modalities are similar, there are variations in choice of first-line therapy. Most pediatric endocrinologists currently recommend thionamide as a first-line treatment.[5] Radioactive iodine has traditionally been used if major side effects are experienced or if the hyperthyroidism does not remit after several years of drug treatment. However, reliable clinical predictors of future relapse after medical therapy are not well established, and radioactive iodine is being increasingly used in some Canadian centres as first-line therapy for adolescents and for patients who have trouble adhering to the medication schedule.[6] Although near-total thyroidectomy is an effective treatment for Graves' disease, it is not recommended for children. However, lifelong monitoring of thyroid function is indicated for children with this disease because of the risks of relapse or hypothyroidism.[7] Young women must be educated about the potential for neonatal Graves' disease in their own children, even if they have been definitively treated with radioactive iodine.

Jennifer Webster
Second-Year Medical Student
Shayne P. Taback
Assistant Professor
Elizabeth A.C. Sellers
Assistant Professor
Heather J. Dean
Professor
Section of Endocrinology and Metabolism
Department of Pediatrics and Child Health
University of Manitoba
Winnipeg, Man.

References
1. Ginsberg J. Diagnosis and management of Graves' disease. *CMAJ* 2003;168(5):575-85.
2. Nordyke RA, Gilbert FI Jr, Harada ASM. Graves' disease: influence of age on clinical findings. *Arch Intern Med* 1988;148:626-31.
3. Segni M, Leonardi E, Mazzoncini B, Pucarelli I, Pasquino AM. Special features of Graves' disease in early childhood. *Thyroid* 1999;9:871-7.
4. Rivkees SA, Sklar C, Freemark M. Clinical review 99: The management of Graves' disease in children, with special emphasis on radioiodine treatment. *J Clin Endocrinol Metab* 1998;83:3767-76.
5. Bergman P, Auldist AW, Cameron F. Review of the outcome of management of Graves' disease in children and adolescents. *J Paediatr Child Health* 2001;37:176-82.
6. Ward L, Huot C, Lambert R, Deal C, Collu R, Van Vliet G. Outcome of pediatric Graves' disease after treatment with antithyroid medication and radioiodine. *Clin Invest Med* 1999;22:132-9.
7. LaFranchi S. Thyroid disease: hyperthyroidism in childhood and adolescence. In: *UpToDate in endocrinology and diabetes*. Version 9.3. Wellesley (Ma): UpToDate; 2001.

Costs of prophylactic resection

In a recent commentary, Steve Morgan and colleagues[1] assess the long-term financial consequences of predictive genetic testing with respect to subsequent diagnostic and preventive services. As they note, prophylactic surgical removal of apparently healthy tissue is one option for prevention of some diseases. Although it has been assumed that such resected tissues are healthy, they may in fact harbour significant histopathologic abnormalities. Histopathologic studies of specimens removed prophylactically from 3 sites (stomach, ovary and colon) illustrate this phenomenon.

Pathologic study identified superficial infiltrates of malignant signet ring cells in 5 of 5 gastrectomy specimens from patients who harboured a germline truncating mutation in the epithelial cadherin (E-cadherin or CDH1) gene.[2] These malignant cells escaped detection by routine pathologic examination, which usually consists of 10 to 15 histopathologic sections, and were detected only through exhaustive histologic sectioning with a minimum of more than 150 sections. Similarly, occult carcinoma of the ovary or fallopian tube was identified in 5 (13%) of 39 prophylactic salpingo-oophorectomy specimens from patients who were positive for germline BRCA.[3] Finally, colectomy specimens from patients with familial risks of colonic cancer may harbour subtle neoplastic changes. In the normal population, 95% of precancerous lesions and early cancers are polypoid in nature, whereas in hereditary nonpolyposis colon cancer these lesions are flat in 50% of cases ("flat adenomas")[4] and can be very difficult to detect. Flat adenomas and cancers are also characteristic of some variants of familial adenomatous polyposis.[5]

The natural history and clinical significance of occult carcinomas from various anatomic sites are not entirely known. Depending on the site, the pathologic detection of an occult carcinoma may alter or determine postoperative adjuvant therapy, follow-up regimens or patient counselling.

In conclusion, surgical pathologic examination of prophylactically removed specimens may reveal occult or minimal lesions. Consequently, such examination must be included as an outcome measure in the implementation of predictive genetic testing programs. In addition, the detection of these small or occult lesions often requires intensive effort. The impact of this effort on work in the surgical pathology laboratory has received scant attention in the predictive genetic testing literature,[6,7] although pathologists are warily anticipating an increase in prophylactic surgery.[8]

Terence J. Colgan
Professor
Robert H. Riddell
Professor
Aaron Pollett
Lecturer
Department of Laboratory Medicine and Pathobiology
University of Toronto
Toronto, Ont.

References
1. Morgan S, Hurley J, Miller F, Giacomini M. Predictive genetic tests and health system costs [editorial]. *CMAJ* 2003;168(8):989-91.
2. Lewis FR, Mellinger JD, Hayashi A, Lorelli D, Monaghan KG, Carneiro F, et al. Prophylactic total gastrectomy for familial gastric cancer. *Surgery* 2001;130:612-9.
3. Colgan TJ, Murphy J, Cole DEC, Narod S, Rosen B. Occult carcinoma in prophylactic oophorectomy specimens. Prevalence and association with BRCA germline mutation status. *Am J Surg Pathol* 2001;25:1283-9.
4. Watanabe T, Muto T, Sawada T, Miyaki M. Flat adenoma as a precursor of colorectal carcinoma in hereditary nonpolyposis colon carcinoma. *Cancer* 1996;77:627-34.
5. Lynch HT, Smyrk TC, Watson P, Lanspa SJ, Lynch PM, Jenkins JX, et al. Hereditary flat adenoma syndrome: a variant of familial adenomatous polyposis. *Dis Colon Rectum* 1992;35:411-21.
6. Miller F, Hurley J, Morgan S, Goeree R, Collins P, Blackhouse G, et al. *Predictive genetic tests and health care costs: final report prepared for the Ontario Ministry of Health and Long-Term Care*. Hamilton (ON): McMaster University, Centre for Health Economics and Policy Analysis; 2002. Available: www.health.gov.on.ca/english/public/pub/ministry_reoirts/geneticsrep02/chepa.html (accessed 2003 May 26).
7. Goel V, for Crossroads 99 Group. Appraising organised screening programmes for testing for genetic susceptibility to cancer. *BMJ* 2001;322:1174-8.
8. Stoler MH. Prophylactic surgical pathology. *Am J Surg Pathol* 2002;26:257-9.

Corrections

In a recently published paper by Louise Séguin and colleagues,[1] the second sentence of the Methods section should read as follows: "For our analyses we used cross-sectional data from the 1998 phase of the Quebec Longitudinal Study of Child Development[54] (QLSCD, conducted by Santé Québec, a division of the Institut de la statistique du Québec) for a sample of 2223 infants whose mean age was 5 months (range 15–36 weeks), corrected for gestational age, at the time of the interview."

Reference
1. Séguin L, Xu Q, Potvin L, Zunzunegui M-V, Frohlich KL. Effects of low income on infant health. *CMAJ* 2003;168(12):1533-8.

In figure 2 of the review article on antiphospholipid syndrome,[1] the word "serum" in all occurences should be replaced with the word "plasma."

Reference
1. Hanly JG. Antiphospholipid syndrome: an overview. *CMAJ* 2003;168(13):1675-82.