AHC Media

Vol. 27, Issue 11, November 2011
www.ahcmedia.com

Clinical Oncology

A monthly update of developments in cancer treatment and research [ALERT]

ABSTRACT & COMMENTARY

Hot Flash Treatment: 2011

By William B. Ershler, MD

SYNOPSIS: In a randomized, double-blind, placebo-controlled trial, clonidine and venlafaxine both proved superior to placebo in reducing hot flashes in breast cancer patients. The study was insufficiently powered to prove superiority of one drug over the other. However, venlafaxine produced earlier reductions and it appeared clonidine had more sustained effect (i.e., at 12 weeks of treatment).

SOURCE: Boekhout AH, et al. Management of hot flashes in patients who have breast cancer with venlafaxine and clinidine: A randomized, double-blind, placebo-controlled trial. *J Clin Oncol* 2011;29:3862-3868.

Hot flashes occur as a common consequence of breast cancer therapy and are quite debilitating for some. Whereas the single most effective treatment is estrogen, this approach is contraindicated in the setting of breast cancer and thus alternative, non-estrogenic approaches have been investigated. Boekhout and colleagues from the Netherlands undertook a double-blind, placebo-controlled randomized trial to compare the efficacy of venlafaxine (Effexor®), clonidine, or placebo in reducing average daily hot flash scores over 12 weeks of treatment.

For this, 102 patients with a history of breast cancer who had been experiencing at least two hot flashes daily were randomly assigned (2:2:1) to venlafaxine 75 mg, clonidine 0.1 mg, or placebo daily for 12 weeks. Patients were stratified by age (≤ 35, 36-50, or > 51 years), duration of complaints (> 9 months or < 9 months), concurrent endocrine therapy (yes or no), and previous chemotherapy (yes or no). Questionnaires at baseline and during treatment assessed daily hot flash scores, sexual function, sleep quality, anxiety, and depression.

After 12 weeks, a total of 80 patients were evaluable for the primary endpoint. During week 12, hot flash scores were significantly lower in the clonidine group vs placebo ($P = 0.03$); for venlafaxine vs placebo, the difference was borderline not significant ($P = 0.07$). However, hot flash scores were equal in the clonidine and venlafaxine groups. Over the course of 12 weeks, the differences between both treatments and placebo were significant ($P < 0.001$ for venlafaxine vs placebo; $P = 0.045$ for clonidine vs placebo).

Financial Disclosure: *Clinical Oncology Alert*'s Editor, William Ershler, MD; peer reviewer, V.R. Veerapalli, MD; executive editor, Leslie Coplin; and managing editor, Neill Kimball report no financial relationships relevant to this field of study.

Clinical Oncology [ALERT]

Clinical Oncology Alert,
ISSN 0886-7186, is published monthly by AHC Media, a division of Thompson Media Group LLC, 3525 Piedmont Road., NE Building 6, Suite 400 Atlanta, GA 30305.

POSTMASTER: Send address changes to Clinical Oncology Alert, P.O. Box 105109, Atlanta, GA 30348.

SUBSCRIBER INFORMATION
1-800-688-2421
customerservice@ahcmedia.com

Editorial E-Mail:
leslie.coplin@ahcmedia.com

Subscription Prices
United States
1 year with free AMA Category 1 credits: $319
Add $17.95 for shipping & handling. (Student/Resident rate: $120). Multiple Copies: Discounts are available for group subscriptions, multiple copies, site-licenses or electronic distribution. For pricing information, call Tria Kreutzer at 404-262-5482. 1-9 additional copies: $215 each; 10 or more copies: $191 each. Back issues: $40 Missing issues will be fulfilled by customer service free of charge when contacted within one month of the missing issue's date.

Canada Add GST and $30 shipping.
Elsewhere Add $30 shipping.
GST Registration Number: R128870672. Periodicals Postage Paid at Atlanta, GA 30304 and at additional mailing offices.

ACCREDITATION
AHC Media is accredited by the Accreditation Council for Continuing Medical Education to provide continuing medical education for physicians.

AHC Media designates this enduring material for a maximum of *25 AMA PRA Category 1 Credits™*. Physicians should claim only the credit commensurate with the extent of their participation in the activity.

This CME activity is intended for the oncologist. It is in effect for 36 months from the date of the publication.

AHC Media

Frequencies of treatment-related adverse effects of nausea, constipation, and severe appetite loss were higher in the venlafaxine group.

COMMENTARY

Both venlafaxine and clonidine previously had been shown to be effective in ameliorating hot flashes,[1-3] and it was hoped that this trial comparing the two drugs (or placebo) over 12 weeks would prove one drug superior. However, what it showed was that both drugs essentially were comparable but that toxicity was somewhat greater with venlafaxine. Venlafaxine produced a more prompt response, but by week 12, hot flashes were fewer in those receiving clonidine. As articulated in the accompanying editorial,[4] the study was insufficiently powered to differentiate the two drugs. By the editorialists' calculations, somewhat more than 150 patients in each of the treatment arms would be required to have a reasonable chance (80%) to detect a difference if it were there. Another concern was that the venlafaxine starting dose (75 mg) is higher than currently recommended (37.5 mg/day, with escalation as tolerated).

Clinicians encounter patients with hot flashes commonly. Venlafaxine and clonidine are two on the list of several (also paroxetine, citalopram, devenlafaxine, gabapentin, pregabalin to name others). None has risen to the top as most efficacious. Dr. Loprinzi and his group at the Mayo Clinic have recommended that a non-hormonal approach start with an antidepressant (e.g., venlafaxine or devenlafaxine) and proceed to one of the antiseizure drugs (e.g., gabapentin) as second line, and that clonidine be used as third line.[4]

In addition to defining the optimal first approach, a number of questions regarding hot flash management are still unanswered. These include whether treatment should be different for those experiencing hot flashes but with no history of breast cancer, or for women who are currently taking tamoxifen? Furthermore, should the same approach be used for the management of hot flashes in men undergoing androgen-ablation therapy for prostate cancer? Although there are notable gaps, the data would currently suggest there are enough similarities to embark on similar approaches for both men and women.[5]

References

1. Goldberg RM, et al. Transdermal clonidine for ameliorating tamoxifen-induced hot flashes. *J Clin Oncol* 1994;12:155-158.
2. Loprinzi CL, et al. Venlafaxine in management of hot flashes in survivors of breast cancer: A randomised controlled trial. *Lancet* 2000;356:2059-2063.
3. Pandya KJ, et al. Oral clonidine in postmenopausal patients with breast cancer experiencing tamoxifen-induced hot flashes: A University of Rochester Cancer Center Community Clinical Oncology Program study. *Ann Intern Med* 2000;132:788-793.
4. Loprinzi CL, et al. Nonestrogenic management of hot flashes. *J Clin Oncol* 2011;29:3842-3846.
5. Loprinzi CL, Wolf SL. Hot flushes: Mostly sex neutral? *Lancet Oncol* 2010;11:107-108.

ABSTRACT & COMMENTARY

Height and Cancer Risk

By William B. Ershler, MD

SYNOPSIS: From a large cohort of women followed prospectively and with an adjunct meta-analysis of existing evaluable studies, a clearly demonstrated, nearly universal (i.e., across tumor types) incremental increase in cancer incidence was observed with advancing height.

SOURCE: Green J, et al. Height and cancer incidence in the Million Women Study: Prospective cohort, and meta-analysis of prospective studies of height and total cancer risk. *Lancet Oncol* 2011;12:785-794.

A number of epidemiological studies have demonstrated an increased risk of cancer in taller people, but it remains unclear if this height-associated risk is cancer-type specific and if it can be accounted for by confounding factors such as socioeconomic status or cigarette smoking. The goal of the current analysis

was to investigate these associations in a large UK prospective cohort with sufficient information on incident cancer to allow direct comparison of height-associated risk across cancer sites and in relation to major potential confounding and modifying factors.

Between 1996 and 2001, 1.3 million middle-aged women with no known prior cancer were enrolled in the UK National Health Service Breast Screening Program (Million Women Study). One aspect of this comprehensive research program was the completion of a recruitment questionnaire that probed characteristics including current height, weight, smoking history, and other social, demographic, and lifestyle factors. A small subset of respondents (n = 3762) were invited to have their height/weight measured at their family physician's office, and these measures correlated remarkably well to earlier self-reports, allowing confidence that the self-reports were valid measures for the population as a whole.

There were 1.3 million women enrolled and followed for a median of 9.4 years (11.7 million person years). During this time, 97,376 new cases of cancer (all sites, other than non-melanoma skin) were diagnosed. The investigators used Cox regression models to calculate adjusted relative risks (RR) per 10 cm increase in measured height for total and site-specific incident cancers, taking attained age as the underlying time variable.

The RR for total cancer was of 1.16 (95% confidence interval [CI] 1.14–1.17; $P < 0.0001$) for every 10 cm increase in height. Risk increased for 15 of the 17 assessed cancer sites and was statistically significant for 10 sites: colon, rectum, malignant melanoma, breast, endometrium, ovary, kidney, central nervous system, non-Hodgkin's lymphoma, and leukemia. The increase in total cancer RR per 10 cm increase in height did not vary significantly by socioeconomic status or by 10 other personal characteristics, but was significantly lower in current than in never smokers ($P < 0.0001$). In current smokers, smoking-related cancers were not as strongly related to height as were other cancers. The investigators also performed a meta-analysis including their findings with 10 other prospective studies, and this demonstrated the height-associated RRs for total cancer varied little across Europe, North America, Australia, and Asia.

COMMENTARY

The current report confirms findings from several smaller studies that cancer incidence increases with increasing adult height.[1-5] Furthermore, because of its large size and careful analysis, it also demonstrated that the height-associated increased risk was relevant to most of the common cancer types, and was apparent even when confounding factors such as socioeconomic status, cigarette smoking, alcohol use, body mass index, age at menarche, parity, and age at first birth were accounted for. Furthermore, combining these data with other published reports in meta-analysis, the relationship of height and total cancer RR is similar in different populations and in both men and women.

[The current analysis demonstrated that taller women tend to have higher socioeconomic status, drink more alcohol, be more active, smoke less, have later menarche, have fewer children, and give birth later in life — all factors that might influence cancer incidence.]

The findings are hypothesis-generating, as there is no clear explanation. Earlier reports that were not quite as robust left the impression that the increased height-associated risk of cancer could be explained by socioeconomic factors or cigarettes.[6,7] Supporting this, the current analysis demonstrated that taller women tend to have higher socioeconomic status, drink more alcohol, be more active, exercise more, smoke less, have later menarche, have fewer children, and give birth later in life — all factors that might influence cancer incidence. Yet, when the data were adjusted for each of these factors (and others) the height-associated risk remained significant. Furthermore, the association is observable for 15 of the 17 most common cancer sites, suggesting a more fundamental mechanism. Identifying this mechanism might provide greater insight into cancer susceptibility. Perhaps it is nothing more than tall people carry a larger cellular load and a correspondingly larger number of targets for cancer development, although this explanation

seems unlikely. Another possibility is that growth promoting factors accounting for increased body stature during development may have residual biological activity upon maturity. Of course, these are conjectural but investigations along those lines would be a logical translation of this interesting and important epidemiological study.

References

1. Albanes D, et al. Adult stature and risk of cancer. *Cancer Res* 1988;48:1658-1662.
2. Batty GD, et al. Adult height in relation to mortality from 14 cancer sites in men in London (UK): Evidence from the original Whitehall study. *Ann Oncol* 2006;17:157-166.
3. Gunnell D, et al. Height, leg length, and cancer risk: A systematic review. *Epidemiol Rev* 2001;23:313-342.
4. Olsen CM, et al. Anthropometric factors and risk of melanoma in women: A pooled analysis. *Int J Cancer* 2008;122:1100-1108.
5. Pischon T, et al. Body size and risk of colon and rectal cancer in the European Prospective Investigation Into Cancer and Nutrition (EPIC). *J Natl Cancer Inst* 2006;98:920-931.
6. Batty GD, et al. Height, wealth, and health: An overview with new data from three longitudinal studies. *Econ Hum Biol* 2009;7:137-152.
7. Sung J, et al. Height and site-specific cancer risk: A cohort study of a korean adult population. *Am J Epidemiol* 2009;170:53-64.

ILLUSTRATIVE CASE SERIES

Mammographic Breast Density and Breast Cancer Risk in Postmenopausal Women

By Jerome W. Yates, MD

Hematology/Immunology Unit, National Institute on Aging, NIH

Dr. Yates reports no financial relationships relevant to this field of study.

Case History

A 66-year-old postmenopausal retired teacher went to her primary care physician because she found a lump in her right breast during a routine bath. The primary care physician was unable to palpate a discrete mass in the area the patient identified and so the patient was referred for a mammogram. Her last mammography was 6 years ago and was normal. The current examination was normal with the exception of the finding that she has bilateral increased density without discrete abnormalities. When advised of the findings by the primary care physician, she said that she had read that dense breasts on mammograms increased the subsequent risk of developing breast cancer. She wanted to know whether she should do something different because of this increased risk.

[A matched controlled study of breast cancer in postmenopausal nurses demonstrated an association between breast density and cancer risk.]

Case Discussion

Breast density decreases as fat replaces glandular and connective tissue in postmenopausal women, while the incidence of breast cancer increases exponentially as women age until the age of about 85 years. A variety of case-control studies have shown that breast cancer risk is correlated with increased mammographic density.[1] The increased risk appears to persist for 10 years or longer in spite of the progressive breast involution following menopause.[2]

A matched controlled study of breast cancer in postmenopausal nurses demonstrated an association between breast density and cancer risk.[3] The association was stronger for cancer in situ than for invasive breast cancer, greater for undifferentiated than well-differentiated invasive cancer, greater for larger than smaller invasive cancers, and more associated with estrogen receptor negative than estrogen receptor positive tumors. Two explanations for the increased association with in situ cancer detection are suggested. The first is that women with dense breasts are more likely to undergo breast biopsies for suspicious lesions resulting in an oversampling and retrieval of a disproportionate number of in situ lesions. The second is that the correlation occurred by chance. The former explanation seems more plausible.

Statistical models for assessing breast cancer risk for younger women have received more attention than for their elderly counterparts. The combination of the "Gail Model" for risk assessment coupled with breast density measures failed to add better definition of breast cancer risk for women of all ages than the Gail model alone.[4] An examination of relative contribution of breast density to the statistical constructs of Gail, Tice, Barlow, and Vermont were explored for women 70 years of age and older.[5] These statistical models were not significantly enhanced by the addition of mammographic breast density in predicting a woman's risk of developing breast cancer.

Recommendations for breast cancer screening for elderly women should continue to be individualized based on their state of health and other influential components of the statistical models: age at menarche, history of postmenopausal estrogen replacement therapy, age when first child was born, history of previous breast biopsies, and body mass index (obesity). These epidemiologic contributions to the assessment of risk for an individual patient still require the guidance of solid clinical judgment from a knowledgeable physician. Mammographic breast density, although associated with the increased risk of breast cancer, contributes little to the modeled aggregation of other associations known to contribute or protect women from developing breast cancer.

References

1. Ginsburg OM, et al. Mammographic density, lobular involution, and risk of breast cancer. *Br J Cancer* 2008;99:1369-1374.
2. Byrne C. Studying mammographic density: Implications for understanding breast cancer. *J Natl Cancer Inst* 1997;89: 531-533.
3. Yaghjyan L, et al. Mammographic breast density and subsequent risk of breast cancer in postmenopausal women according to tumor characteristics. *J Natl Cancer Inst* 2011;103:1179-1189.
4. Tice JA, et al. Mammographic breast density and the Gail model for breast cancer risk prediction in a screening population. *Breast Cancer Res Treat* 2005;94:115-122.
5. Vacek PM, et al. Breast cancer risk assessment in women aged 70 and older. *Breast Cancer Res Treat* 2011;130:291-299.

ABSTRACT & COMMENTARY

The Risk of Surveillance vs Lymph Node Dissection in Germ Cell Cancer: The Occurrence of Second Malignancy

By William B. Ershler, MD

SYNOPSIS: In an epidemiologic analysis of SEER data, middle-aged patients with early-stage disease who opted for active surveillance rather than retroperitoneal lymph node dissection experienced a greater rate of second malignancy. The investigators speculate that this may relate to increased radiation exposure (multiple CT scans) and a greater likelihood of subsequent chemotherapy use.

SOURCE: Chamie K, et al. Secondary malignancies among nonseminomatous germ cell tumor cancer survivors. *Cancer* 2011;117: 4219-4230.

For patients who present with stage I nonseminomatous germ cell tumor (NSGCT) there is an approximate 70% cure rate by orchiectomy alone.[1] The implication is that the initial staging evaluation understages approximately 30% and therein lies the rationale for retroperitoneal lymph node dissection (RPLND). However, RPLND has been associated with long-term consequences impinging upon quality of life, and for the past two decades approximately one-half of patients with stage I disease elect to pursue a course of active surveillance rather than undergo immediate surgery.[2] In recognition of this, the National Comprehensive Cancer Network (NCCN) recommends that early-stage NSGCT patients who forego RPLND have CT imaging every 2-3 months for the first year, every 3-4 months for the second year, every 4 months for the third year, every 6 months for the fourth year, and annually thereafter. Compliance with this recommendation translates into an average of 13-15 CT scans in the first 5 years, thereby realizing a not inconsequential cumulative radiation exposure of over 200 millisieverts (20 rem). This exposure may result in long-term sequelae, most notably the occurrence of second malignancy. In the current study, Chamie and co-investigators sought to identify whether there was an increased risk of second cancers among patients who chose initial surveillance for NSGCT.

The authors utilized data from the Surveillance, Epidemiology, and End Results (SEER) program and stratified the cohort based on whether they underwent RPLND. Within the SEER database they were able to identify 7301 men with NSGCT (all stages) diagnosed between 1988 and 2006. In that cohort, 84 men developed second malignancy. A propensity-score model was used to adjust for covariates, and a competing risks regression analysis was performed to estimate cumulative incidence rates of second malignancy. Incidence risk ratios were predicted by using the cumulative incidence rates per 10,000 patients.

There was no statistically significant increase in the incidence of a secondary malignancy for the entire cohort of testicular cancer survivors. However, when the analysis was restricted only to stage I patients older than 45 years, nonsurgical management was an independent predictor of developing a second malignancy. Extrapolation of these data would allow the prediction that for every 10,000 patients with stage I NSGCT who chose to forego RPLND, an absolute excess incidence of 22, 52, and 73 secondary malignancies would be diagnosed at 5 years, 10 years, and 15 years, respectively.

[These findings raise the specter of concern that nonsurgical management of NSGCT may be associated with more health risks than primary PRLND.]

COMMENTARY

The current results indicated that patients aged > 45 years who forego RPLND for stage I NSGCT are more likely to develop a second malignancy than those who undergo RPLND. Whether this is the result of exposure to radiation (multiple CTs) or a greater exposure to chemotherapy among those who choose initial nonsurgical approach, to both, or to neither remains to be clarified. It is curious that these differences were not apparent for younger patients. Possibly low levels of radiation have less carcinogenic effect when exposed at a younger age, although it is also possible that second cancers will occur over a longer time period than that encompassed in this study. Nonetheless, it is not unheard of to observe different age-associated risks to radiation exposure. For example, in an analysis of close to 50,000 atomic bomb survivors, for those exposed to 0.5-1.0 grays, peak cancer incidence was observed to be highest in those exposed between the ages of 20-29.[3] There are a number of variables that may be at play that could not be accounted for using the SEER data alone. For example, what percentage of those under surveillance actually complied with the CT scanning schedule, how many in each group received chemotherapy and with what agents, and were there risk factors or comorbitities that pertained to the decision to forego initial surgery that might portend second malignancy? Were there more cigarette smokers with lung disease who opted for surveillance who subsequently developed lung cancer catalogued as a second malignancy? Finally, with regard to radiation exposure, the question arises whether newer machines with exposure to lower doses will be equally effective as instruments of surveillance and whether such will reduce risk for second cancers.

Nonetheless, what is presented is provocative. The findings raise the specter of concern that nonsurgical management of NSGCT may, in the long run, be associated with more health risks than primary RPLND.

References

1. Koch MO. Cost-effective strategies for the follow-up of patients with germ cell tumors. *Urol Clin North Am* 1998;25:495-502.
2. Osswald M, et al. Treatment of a population based sample of men diagnosed with testicular cancer in the United States. *Urol Oncol* 2009;27:604-610.
3. Preston DL, et al. Solid cancer incidence in atomic bomb survivors: 1958-1998. *Radiat Res* 2007;168:1-64.

CME Instructions

To earn credit for this activity, please follow these instructions:

1. Read and study the activity, using the provided references for further research.
2. Log on to www.cmecity.com to take a post-test; tests can be taken after each issue or collectively at the end of the semester. First-time users will have to register on the site using the 8-digit subscriber number printed on their mailing label, invoice or renewal notice.
3. Pass the online tests with a score of 100%; you will be allowed to answer the questions as many times as needed to achieve a score of 100%.
4. After successfully completing the last test of the semester, your browser will be automatically directed to the activity evaluation form, which you will submit online.
5. Once the completed evaluation is received, a credit letter will be e-mailed to you instantly.

CME Objectives

Upon completion of this educational activity, participants should be able to:

- discuss the most recent information regarding diagnosis and treatment of various types of cancer;
- describe current prevalence/surveillance data and long-term follow-up results of chemotherapy/radiation regimens;
- describe new advances in the field of oncology.

CME Questions

1. From the randomized trial of venlafaxine and clonidine for hot flash treatment, which of the following conclusions *cannot* be drawn?

a. Both drugs were superior to placebo in controlling hot flashes.
b. Venlafaxine produced more prompt reduction in hot flashes.
c. Clonidine treatment resulted in fewer hot flashes in the 12th week.
d. Based upon the findings for all 12 weeks, venlafaxine was superior to clonidine for the treatment of hot flashes.

2. Breast density presents increased risk for:

a. in situ rather than invasive cancer.
b. well-differentiated rather than undifferentiated cancer.
c. smaller rather than larger invasive cancers.
d. ER positive rather than ER negative cancers.

3. The height-associated increased relative risk for the development of cancer:

a. is apparent for most tumor types.
b. cannot be explained simply by socioeconomic status.
c. cannot be explained by cigarette smoking (current, ever, or never).
d. is apparent in both men and women.
e. All of the above

4. Which patients with nonseminomatous germ cell tumors have a greater risk of second malignancy?

a. Patients diagnosed at age 25 with stage I disease who undergo initial RPLN dissection.
b. Patients diagnosed at age 45 with stage I disease who do not undergo initial RPLN dissection.
c. Patients diagnosed at age 25 with stage III disease who do not undergo initial RPLN dissection.
d. Patients diagnosed at age 45 with stage III disease who do not undergo initial RPLN dissection.

United States Postal Service

Statement of Ownership, Management, and Circulation

1. Publication Title	2. Publication Number	3. Filing Date
Clinical Oncology Alert	0 8 8 6 – 7 1 8 6	10/1/11
4. Issue Frequency	5. Number of Issues Published Annually	6. Annual Subscription Price
Monthly	12	$319.00

7. Complete Mailing Address of Known Office of Publication *(Not printer) (Street, city, county, state, and ZIP+4)*
3525 Piedmont Road, Bldg. 6, Ste. 400, Atlanta, Fulton County, GA 30305

Contact Person: Robin Salet
Telephone: 404-262-5489

8. Complete Mailing Address of Headquarters or General Business Office of Publisher *(Not printer)*
3525 Piedmont Road, Bldg. 6, Ste. 400, Atlanta, GA 30305

9. Full Names and Complete Mailing Addresses of Publisher, Editor, and Managing Editor *(Do not leave blank)*

Publisher *(Name and complete mailing address)*
James Still, President and CEO
AHC Media LLC, 3525 Piedmont Road, Bldg. 6, Ste. 400, Atlanta, GA 30305

Editor *(Name and complete mailing address)*
Leslie Coplin, same as above

Managing Editor *(Name and complete mailing address)*
Neill Kimball, same as above

10. Owner *(Do not leave blank. If the publication is owned by a corporation, give the name and address of the corporation immediately followed by the names and addresses of all stockholders owning or holding 1 percent or more of the total amount of stock. If not owned by a corporation, give the names and addresses of the individual owners. If owned by a partnership or other unincorporated firm, give its name and address as well as those of each individual owner. If the publication is published by a nonprofit organization, give its name and address.)*

Full Name	Complete Mailing Address
Ableco, LLC	299 Park Avenue, New York, NY 11201
GSC, LLC	500 Campus Drive, Florham Park, NJ 07932
Natixis	9 West 57th Street, 35th Floor, New York, NY 10019
NewStar Financial, Inc.	500 Boylston Street, Suite 1250, Boston, MA 02116
Fortress	1345 Avenue of the Americas, 46th Floor, New York, NY 10105
PNC	1600 Market Street, Philadelphia, PA 19103

11. Known Bondholders, Mortgagees, and Other Security Holders Owning or Holding 1 Percent or More of Total Amount of Bonds, Mortgages, or Other Securities. If none, check box → ☐ None

Full Name	Complete Mailing Address
Thompson Publishing Group Inc.	805 15th Street, NW, 3rd Floor, Washington, D.C. 20005

12. Tax Status *(For completion by nonprofit organizations authorized to mail at nonprofit rates) (Check one)*
The purpose, function, and nonprofit status of this organization and the exempt status for federal income tax purposes:
☑ Has Not Changed During Preceding 12 Months
☐ Has Changed During Preceding 12 Months *(Publisher must submit explanation of change with this statement)*

PS Form **3526**, October 1999 *(See Instructions on Reverse)*

13. Publication Title: Clinical Oncology Alert			14. Issue Date for Circulation Data Below: September 2011	
15.		Extent and Nature of Circulation	Average No. Copies Each Issue During Preceding 12 Months	No. Copies of Single Issue Published Nearest to Filing Date
a.		Total Number of Copies *(Net press run)*	367	338
b. Paid and/or Requested Circulation	(1)	Paid/Requested Outside-County Mail Subscriptions Stated on Form 3541. *(Include advertiser's proof and exchange copies)*	194	195
	(2)	Paid In-County Subscriptions Stated on Form 3541 *(Include advertiser's proof and exchange copies)*	0	0
	(3)	Sales Through Dealers and Carriers, Street Vendors, Counter Sales, and Other Non-USPS Paid Distribution	20	19
	(4)	Other Classes Mailed Through the USPS	23	5
c.		Total Paid and/or Requested Circulation *(Sum of 15b. (1), (2),(3),and (4))* ▶	237	219
d. Free Distribution by Mail *(Samples, compliment ary, and other free)*	(1)	Outside-County as Stated on Form 3541	4	4
	(2)	In-County as Stated on Form 3541	0	0
	(3)	Other Classes Mailed Through the USPS	0	0
e.		Free Distribution Outside the Mail *(Carriers or other means)*	20	20
f.		Total Free Distribution *(Sum of 15d. and 15e.)* ▶	24	24
g.		Total Distribution *(Sum of 15c. and 15f)* ▶	261	243
h.		Copies not Distributed	106	95
i.		Total *(Sum of 15g. and h.)* ▶	367	338
j.		Percent Paid and/or Requested Circulation *(15c. divided by 15g. times 100)*	91%	90%

16. Publication of Statement of Ownership
☑ Publication required. Will be printed in the November 2011 issue of this publication. ☐ Publication not required.

17. Signature and Title of Editor, Publisher, Business Manager, or Owner — Date: 09/12/11

I certify that all information furnished on this form is true and complete. I understand that anyone who furnishes false or misleading information on this form or who omits material or information requested on the form may be subject to criminal sanctions (including fines and imprisonment) and/or civil sanctions (including civil penalties).

Instructions to Publishers

1. Complete and file one copy of this form with your postmaster annually on or before October 1. Keep a copy of the completed form for your records.
2. In cases where the stockholder or security holder is a trustee, include in items 10 and 11 the name of the person or corporation for whom the trustee is acting. Also include the names and addresses of individuals who are stockholders who own or hold 1 percent or more of the total amount of bonds, mortgages, or other securities of the publishing corporation. In item 11, if none, check the box. Use blank sheets if more space is required.
3. Be sure to furnish all circulation information called for in item 15. Free circulation must be shown in items 15d, e, and f.
4. Item 15h., Copies not Distributed, must include (1) newsstand copies originally stated on Form 3541, and returned to the publisher, (2) estimated returns from news agents, and (3), copies for office use, leftovers, spoiled, and all other copies not distributed.
5. If the publication had Periodicals authorization as a general or requester publication, this Statement of Ownership, Management, and Circulation must be published; it must be printed in any issue in October or, if the publication is not published during October, the first issue printed after October.
6. In item 16, indicate the date of the issue in which this Statement of Ownership will be published.
7. Item 17 must be signed.

Failure to file or publish a statement of ownership may lead to suspension of Periodicals authorization.

PS Form **3526**, October 1999 *(Reverse)*

PHARMACOLOGY WATCH

Supplement to *Clinical Cardiology Alert, Clinical Oncology Alert, Critical Care Alert, Hospital Medicine Alert, Infectious Disease Alert, Internal Medicine Alert, Neurology Alert, OB/GYN Clinical Alert, Primary Care Reports, Travel Medicine Advisor.*

Medication Poisonings Are Increasing in Children

In this issue: Medication poisonings in children; rosuvastatin vs atorvastatin for atherosclerosis; saw palmetto for prostate symptoms; using atypical antipsychotics for off-label indications in adults; and FDA actions.

More medications, more poisonings

Medication poisonings among young children have increased in frequency in recent years despite safety measures to prevent them, according to a new study from *Pediatrics*. Researchers used patient records of more than 450,000 children 5 years old or younger from 2001-2008. The rate of poisoning increased by about a third during this time span compared to the prior decade. Child self-exposure was responsible 95% of the time with ingestion of prescription drugs causing more than half of the poisonings and more than 70% of significant injuries. The most dangerous drugs were opioids, sedative-hypnotics, and cardiovascular agents. The authors conclude that the number of children visiting emergency departments after medication exposure is increasing, with the majority of ingestions caused by children finding and ingesting medications by themselves. They suggest that efforts at poison-proofing homes with young children "may be a good, but insufficient, strategy." They further suggest that the increase in poisonings is in part due to the rise in number of medications in the environments of young children, with the number of adults taking medications, especially opioid medications, rising dramatically in the last 10 years. Other possible explanations include more siblings on medications, especially ADHD meds, as well as exposure to grandparents' homes where child-proofing may not be as rigorous. They further conclude that current preventive efforts are inadequate and new measures, such as efforts targeting home medication safety (including storage of medications and child-resistant closures) and repackaging (such as blister packs and flow restrictors on liquid medications), should be considered. (*Pediatrics* published online September 16, 2011.) ■

Rosuvastatin no better than atorvastatin

Rosuvastatin is no better than atorvastatin in slowing progression of coronary atheroma, according to AstraZeneca, the manufacturer of rosuvastatin and sponsor of the study. Researchers compared rosuvastatin 40 mg to atorvastatin 80 mg in the Study of Coronary Atheroma by Intravascular Ultrasound: Effect of Rosuvastatin vs Atorvastatin (SATURN) trial. The primary efficacy endpoint was change from baseline in percent atheroma volume in a targeted coronary artery as assessed by intravascular ultrasound. After 104 weeks of treatment in some 1300 patients, there was a numerical greater reduction in favor of rosuvastatin, but the reduction did not reach statistical significance (astrazeneca.com/Media/Press-releases). The full results will be presented at the American Heart Association meeting in

This supplement was written by William T. Elliott, MD, FACP, Chair, Formulary Committee, Kaiser Permanente, California Division; Assistant Clinical Professor of Medicine, University of California-San Francisco. In order to reveal any potential bias in this publication, we disclose that Dr. Elliott reports no consultant, stockholder, speaker's bureau, research, or other financial relationships with companies having ties to this field of study. Questions and comments, call: (404) 262-5404. E-mail: neill.kimball@ahcmedia.com.

November. The results come as a blow to the manufacturer of rosuvastatin (Crestor) who had hoped to gain a marketing advantage before the introduction of low-cost generic atorvastatin into the market, slated for December. ■

Saw palmetto for prostate symptoms

Saw palmetto is ineffective for treating lower urinary tract symptoms (LUTS) in men with benign prostatic hyperplasia (BPH), even at higher doses, according to a new study. Previous studies have shown no benefit from saw palmetto, but researchers in this current study set out to test the efficacy of 2-3 times the normal daily dose on men over the age of 45 with significant LUTS. The main outcome was the difference in American Urologic Association Symptom Index score between baseline and week 72. Both saw palmetto and placebo led to an improvement in symptoms with a favorability toward placebo regardless of the dose of saw palmetto. Doses tested were a single 320 mg tablet per day with dose escalation to 2, then 3, tablets per day. The authors conclude that increasing doses of saw palmetto root extract did not lower LUTS more than placebo in men with BPH (*JAMA* 2011;306:1344-1351). This is the second rigorously controlled trial after the Saw Palmetto Treatment for Enlarged Prostates study (*N Engl J Med* 2006;354:557-566) to show no benefit from the supplement on LUTS in men with BPH. ■

Off-label use of atypical antipsychotics

Controversy surrounds the use of atypical antipsychotics for off-label indications in adults, especially the elderly with dementia. A new meta-analysis reviews the evidence of efficacy of these drugs for various off-label uses. Of more than 12,000 studies considered, 162 were included in the analysis. Drugs reviewed included risperidone (Risperdal), olanzapine (Zyprexa), quetiapine (Seroquel), aripiprazole (Abilify), ziprasidone (Geodon), asenapine (Saphris), iloperidone (Fanapt), and paliperidone (Invega). For elderly patients with dementia, a small but statistically significant improvement in symptoms such as psychosis, mood alterations, and aggression were seen with aripiprazole, olanzapine, and risperidone. For generalized anxiety disorder, quetiapine was the most effective, while for obsessive-compulsive disorder, risperidone was associated with a 3.9 greater likelihood of favorable response, compared with placebo when used with antidepressants. There was no benefit seen with any of the drugs used in treating eating disorders, substance abuse, or insomnia, and only marginal benefit in personality disorders or posttraumatic stress disorder. All of these drugs have a boxed warning regarding increased mortality in elderly patients with dementia and increased risk of suicidality. Increased risk of death was seen in elderly patients with a number needed to harm (NNH) of 87. Also noted was increased risk of stroke, especially with risperidone (NNH = 53), extraparametal symptoms (NNH = 10 for olanzepine, NNH = 20 for risperidone), and urinary tract symptoms (NNH range = 16-36). Weight gain was also a problem in non-elderly adults, particularly with olanzapine (incidence of more than 40%), while akathisia was more common with aripiprazole. Other common side effects included fatigue, sedation, and extrapyramidal symptoms. (*JAMA* 2011;306:1359-1369). ■

FDA actions

The FDA has issued a warning regarding the potential for arrhythmia associated with the antinausea drug ondansetron (Zofran). The drug should be avoided in patients with QT prolongation as they are at particular risk of developing torsade de pointes. Ondansetron should be used with caution in patients with congestive heart failure, bradyarrhythmias, those predisposed to low potassium or magnesium, and in those taking drugs that cause QT prolongation. These patients should have electrocardiogram monitoring if ondansetron is indicated. The FDA is requiring new labeling changes to reflect these warnings.

The FDA is reminding physicians and patients that epinephrine inhaler (Primatene Mist), the only over-the-counter inhaler for asthma, will be removed from the market on December 31. The withdrawal is due to an international ban on chlorofluorocarbon propellant. The FDA is recommending that physicians ask their patients with asthma if they use Primatene Mist and talk to them about prescription alternatives.

The FDA has approved infliximab (Remicade) to treat moderate-to-severe ulcerative colitis (UC) in children 6 years and older who have had inadequate response to conventional therapy. The drug is already approved for adults with UC. The approval was based on a randomized, open-label trial of 60 children ages 6 to 17 with moderate-to-severe UC. The drug carries a boxed warning for serious infections and cancer. Infliximab is manufactured by Janssen Biotech. ■

Clinical Briefs in Primary Care™

The essential monthly primary care update

By Louis Kuritzky, MD

Supplement to *Clinical Cardiology Alert, Clinical Oncology Alert, Critical Care Alert, Hospital Medicine Alert, Infectious Disease Alert, Neurology Alert, OB/GYN Clinical Alert, Primary Care Reports.*

VOLUME 16, NUMBER 11 PAGES 21-22 NOVEMBER 2011

How Often Do You Really Have to See Patients on Warfarin?

Source: Rose AJ, et al. *Chest* 2011;140: 359-365.

IT HAS BEEN CUSTOMARY TO ASK PATIENTS on warfarin, once controlled and stable, to return on a monthly basis for recheck. This interval has been based on tradition, rather than any firm scientific basis. Frequent visits in otherwise stable patients present a significant burden of time, cost, inconvenience, and even the opportunity for overzealous "fine tuning," and may not enhance the amount of time spent in the therapeutic range. It would, therefore, be desirable to have better insight into whether stable patients might be safely allowed longer intervals without risking either toxicity of supratherapeutic warfarin dose, or thrombotic risk of subtherapeutic levels.

Rose et al report on data obtained from a large population of persons receiving anticoagulation from the U.S. Veterans hospital system (n = 104,451). By comparing the interval between an in-range international normalized ratio (INR) and the next INR measurement with the likelihood of being in the therapeutic range on follow-up visit, they were able to discern that the first two visits after a therapeutic INR measurement are time sensitive: that is, extending the time until next follow-up beyond 4 weeks was associated with progressively greater likelihood of finding an out-of-range INR at the next visit. This relationship, however, was not seen in persons with consistently in-range INR readings, i.e., if a patient had experienced three consecutive INR in-range visits, extending the length of time until next follow-up was not associated with greater likelihood of an out-of-range INR.

At the current time, another trial comparing monthly with quarterly INR monitoring is underway. Pending results from that trial, this evidence suggests that until patients have at least three consecutive stable INR measurements, the traditional 4-week return policy is best. After that, a longer interval until next INR measurement is acceptable, but has only been studied as far out as 38 days. ■

Replacing Carbohydrates with Nuts in the Diabetic Diet

Source: Jenkins DJ, et al. *Diabetes Care* 2011;34:1706-1711.

CONSUMPTION OF NUTS, ESPECIALLY WALnuts, has been associated with favorable health outcomes. For diabetics, maintenance of a healthy body weight, reduction of high-glycemic index foods, and lipid modulation through diet are each a potentially critical consideration. Because nuts have significant fat content, there has been concern that were diabetics to substitute nuts for other carbohydrates, a detrimental impact on either weight or lipids might be seen.

Jenkins et al randomized type 2 diabetics (n = 117) to substitute carbohydrates in their diets in one of three ways: mixed nut replacement, muffin replacement, or half-and-half nuts plus muffins. Based on energy requirements calculated with the Harris-Benedict equation, participants were asked to substitute their prescribed replacement supplement for whatever carbohydrate had previously comprised an equal caloric proportion of their diet. For instance, a person requiring 1600-2400 kcal/d was given 475 kcal of a replacement supplement. The trial lasted 3 months. The nut mix consisted of almonds, pistachios, walnuts, pecans, hazelnuts, peanuts, cashews, and macadamias. The muffin was whole wheat, with no sugar added. The absolute kcal content of the supplement was the same whether administered as nuts, muffin, or mixed.

The group supplemented with nuts enjoyed a statistically significant A1c reduction of 0.21%, but no significant A1c change was seen in the other two groups. Similarly, cholesterol, LDL, and cholesterol:HDL ratios were most favorably affected by the nut supplement. Nut replacement for carbohydrates has favorable effects in type 2 diabetes. ■

Hypertensive Emergency: The Prognostic Value of Elevated Troponins

Source: Afonso L, et al. *J Clin Hypertens* 2011;13:551-556.

HYPERTENSIVE EMERGENCY, CHARACTERized by marked elevation of blood pressure (typically > 180/120) associated with signs of target organ damage, is a common presenting issue in emergency departments. Since cardiac toxicity may be one of the signs of target organ damage, troponins are often measured, even though there may be no symptoms of myocardial ischemia or signs on EKG. Especially when troponins are measured in acute coronary syndromes, they have strong prognostic value. Whether they provide any discriminative value in per-

sons with hypertensive emergency has not been previously well-studied.

A retrospective analysis was done on all patients with hypertensive emergency seen at two inner-city population hospitals in Detroit (n = 567) in whom troponins had been measured. Among this group, one-third demonstrated troponin elevation (mean peak = 4.06 ng/mL). However, follow-up of these patients did not find that the presence or degree of elevation of troponins predicted subsequent mortality over the next 3 years.

Elevation of troponins is commonly seen in patients with hypertensive emergency, but in the absence of an acute coronary syndrome, is not prognostically valuable. ■

Is Mercury Really a Bad Guy in CV Disease?

Source: Houston MC. *J Clin Hypertens* 2011;13:621-627.

Mercury has a bad rap sheet: it decreases cellular oxidative defenses, increases oxidative stress, reduces the effectiveness of metalloenzymes, induces mitochondrial dysfunction, increases vascular inflammation, and worsens endothelial function. In addition, mercury toxicity is associated with increased carotid intima-media thickness. Omega-3 fatty acids, as contained in fish, can antagonize some of the detrimental effects of mercury. However, fish in the diet are also currently the major source of human exposure to mercury.

There is no known biologic or physiologic role of mercury in the body, hence it must be regarded as a toxin.

Observational data generally, but inconsistently, find an association between tissue levels of mercury and cardiovascular disease. For hypertension particularly, numerous different populations have found a relationship between tissue mercury levels and blood pressure (systolic, diastolic, and pulse pressure). Chronic mercury toxicity may be inexpensively measured by a 24-hour urine mercury level. The author does not include mention of any trials indicating favorable effects achieved by modulation of mercury, although selenium, by complexing with mercury, may mollify some of its toxic effects. ■

Long-Term Azithromycin for Prophylaxis of COPD Exacerbations

Source: Albert RK, et al. *N Engl J Med* 2011;365:689-698.

For many patients with moderate-severe chronic obstructive pulmonary disease, acute exacerbations (AECOPD) are highly problematic. For hospitalized AECOPD, the mortality rate is approximately 10%; loss of pulmonary function that typically accompanies an AECOPD is usually not regained; mortality during the year following an AECOPD is increased. Hence, reduction and/or delay of AECOPD is an important goal.

Macrolides are often the antimicrobial agents chosen to treat AECOPD. This trial in patients with COPD randomized subjects to azithromycin 250 mg qd (n = 570) or placebo (n = 572) for 1 year. The patient's background COPD treatments were unchanged. The primary outcome of the trial was time to first AECOPD. Secondary outcomes included QOL, and scores on the St. Georges Respiratory Questionnaire. More than three-fourths of study participants were receiving background inhaled steroids, long-acting beta agonists, and/or long-acting anticholinergics during the trial.

Azithromycin prophylaxis was associated with a statistically significant prolongation of time to first AECOPD, as well as a 27% relative-risk reduction in the frequency of AECOPD. The St. George's Respiratory Questionnaire scores were improved significantly more in the azithromycin group. One adverse effect analyzed was affect on hearing function: Azithromycin was associated with a slightly higher incidence of hearing decrement than placebo. However, improvements in hearing noted on follow-up occurred whether the drug was discontinued, suggesting that perhaps the incidence of hearing decrements were initially overestimated.

Azithromycin prophylaxis may provide important benefits in COPD, especially for persons with frequent AECOPD. ■

Unintended Medication Consequences of Hospital Admission

Source: Bell CM, et al. *JAMA* 2011;306: 840-847.

Most hospitalizations have a focused agenda: heart failure, pneumonia, acute trauma, etc. It is not at all difficult to conceive that as a consequence of intensified focus on one or more often acute problems, attention can be drawn away from the issues of lesser acuity, such as maintenance medications for dyslipidemia, dysglycemia, or thyroid disease. Sometimes because of discontinuity between persons involved in the patient's hospitalization and outpatient providers, inadvertent discontinuation of necessary chronic medications can be overlooked.

Using the database of patients in Ontario, Canada (n = 396,380; age 66 and older), Bell et al examined prescription data to see whether chronic medications from five different classes experienced discontinuation subsequent to hospitalization. The five classes were: statins, antiplatelet/anticoagulants, levothyroxine, respiratory inhalers, and gastric acid inhibitors.

Hospitalization was associated with an increased incidence of discontinuation of all five classes of agents. Hospitalization, which included ICU admission, was disproportionately likely to be associated with chronic medication discontinuation. Equally distressing, the data demonstrated an increased risk for death or subsequent hospitalization in persons who discontinued their chronic medications. Gaps in continuity of care are of significant consequence to hospitalized patients. ■

Clinical Briefs in Primary Care™ is published monthly by AHC Media.

Executive Editor: Leslie Coplin.
Editor: Stephen Brunton, MD.
Managing Editor: Neill L. Kimball.
This is an educational publication designed to present scientific information and opinion to health professionals, stimulate thought, and further investigation. It does not provide advice regarding medical diagnosis or treatment for any individual case. It is not intended for the layman.

Subscriber Information
Customer Service: 1-800-688-2421
E-Mail Address: neill.kimball@ahcmedia.com
World Wide Web: www.ahcmedia.com
Address Correspondence to: AHC Media, 3525 Piedmont Road, Building Six, Suite 400, Atlanta, GA 30305.

AHC Media