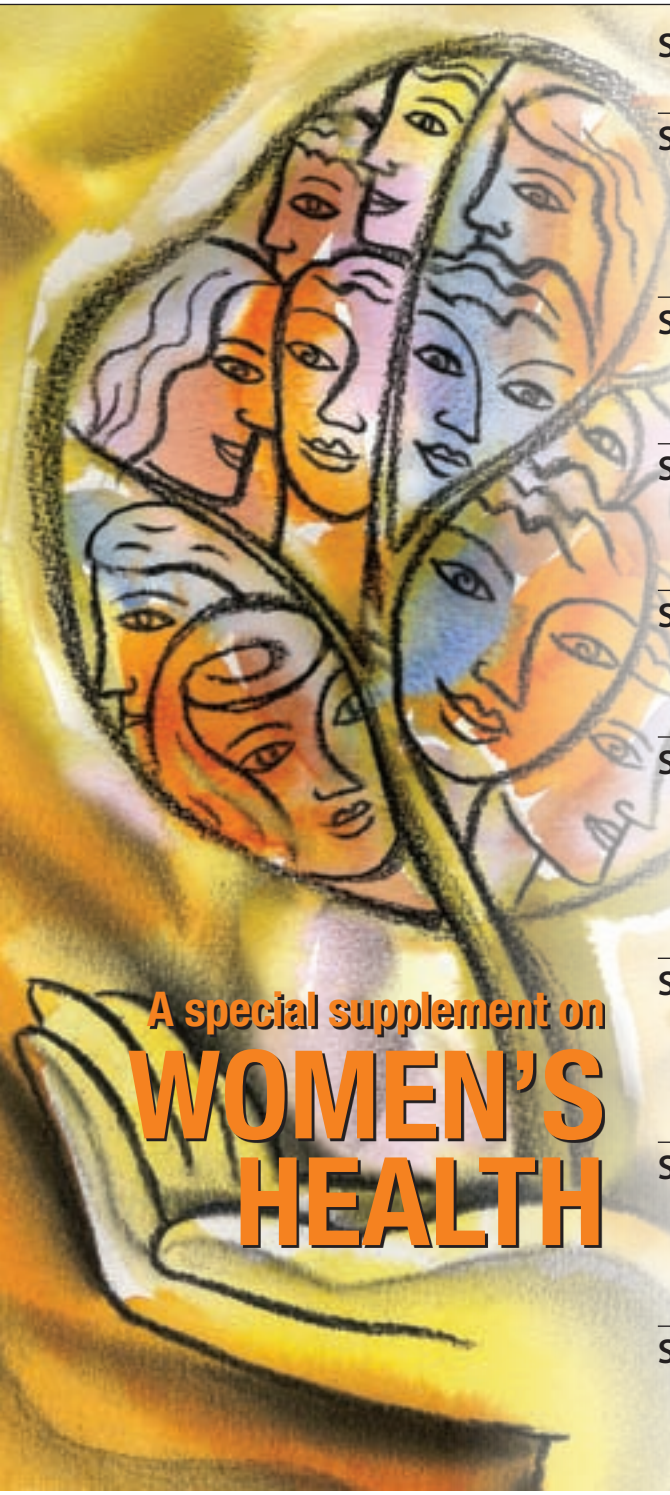
This supplement was sponsored by Primary Care Education Consortium and Primary Care Metabolic Group. It was edited and peer reviewed by *The Journal of Family Practice*.

PRIMARY CARE EDUCATION CONSORTIUM
WWW.PCECONSORTIUM.ORG

PCMG Primary Care Metabolic Group
WWW.PCMG-US.ORG

SUPPLEMENT TO
THE JOURNAL OF
FAMILY PRACTICE

VOL 63, NO 2 | FEBRUARY 2014 | www.jfponline.com



A special supplement on
WOMEN'S HEALTH

This supplement is jointly sponsored by Allergan, Inc.; AstraZeneca; Duchesnay USA; Horizon Pharma, Inc.; and Novo Nordisk, Inc.

Introduction

Stephen A. Brunton, MD, FAAFP

Two decades ago, the American Medical Association found evidence indicating that gender disparities occurred in clinical practice and urged physicians to take appropriate action.[1] A decade later, the Institute of Medicine called for a better understanding of the differences between women and men, beyond the known biological differences, and that this understanding be integrated into clinical practice.[2]

And yet gender-related differences remain. The crude mortality rate for ischemic heart disease-related deaths declined 36.3% for women and 26.5% for men from 2000 to 2009.[3] In 2010, the hospitalization rate for diabetes-related problems was half the rate in women as in men.[4] Women are more likely to experience more severe rheumatoid arthritis, with worse disability and pain, compared to men.[5,6] Women are also more likely than men to receive potentially inappropriate medications (18.1% vs 11.8%)[4] and to have less positive experiences while hospitalized.[7]

While better appreciated than 2 decades ago, gender-related differences remain an important issue in clinical practice. This supplement includes 8 articles that focus on the needs and considerations in providing care to women.

In the first of several articles that focus on cardiometabolic diseases, Dr. JoAnne Foody reviews clinical experience with the 2 newest antiplatelet agents, prasugrel and ticagrelor, in the management of women with acute coronary syndrome. Recommendations regarding transition of care following hospitalization are also provided. Dr. Michael Cobble focuses on patient assessment and treatment strategies for primary prevention of coronary heart disease in women. Succinct recommendations are provided to help women modify abnormal lipid levels and blood pressure as well as stop smoking. Drs. Donna Ryan and Jill Braverman-Panza highlight overarching principles in the management of overweight or obesity in women. In addition to key considerations in assessment, the contemporary management of overweight and obesity in primary care is described. Dr. Penny Tenzer-Iglesias describes key risk factors for type 2 diabetes mellitus in women as well as important complications, such as cardiovascular disease and sexual and urologic problems. The implications of psychosocial well-being, benefits of self-care, and coping strategies in women with type 2 diabetes mellitus are also provided.

Dr. Gary Ruoff summarizes the contemporary management of early rheumatoid arthritis in women in primary care, with a focus on the role of corticosteroids and nonsteroidal anti-inflammatory drugs. Drs. Jennifer Niebyl and Gerald Briggs outline the assessment and management of women with pregnancy-related nausea and vomiting. The roles of nonpharmacologic and pharmacologic options are discussed, including the reintroduction in the United States of doxylamine succinate/pyridoxine hydrochloride. Dr. Pamela Ellsworth reviews the symptom complex of idiopathic overactive bladder and the importance of behavioral modification as first-line therapy. The selection and use of antimuscarinic agents are reviewed and details provided about the 2 newest treatment options, mirabegron and onabotulinumtoxinA. Finally, Dr. Roger Cady discusses migraine headaches in women and the characteristics that differentiate chronic migraine from episodic migraine. Dr. Cady reviews the limited evidence regarding abortive and preventive pharmacologic treatment of chronic migraine, with additional approaches based on his experience.

It is my hope that the insights provided by the authors will be helpful to family physicians in managing their female patients with these common diseases.

Stephen A. Brunton, MD, FAAFP, Adjunct Clinical Professor, Department of Family Medicine, University of North Carolina, Chapel Hill, NC; Executive Vice President for Education, Primary Care Education Consortium, Charlotte, NC

DISCLOSURES

Dr. Brunton discloses that he is on the advisory boards for Abbott Laboratories; AstraZeneca; Boehringer-Ingelheim GmbH; Eli Lilly and Company; Janssen Pharmaceuticals, Inc.; Novartis Pharmaceuticals Corporation; Novo Nordisk, Inc.; Sanofi US; and Teva Pharmaceuticals USA, Inc. He is on the speakers' bureaus for Boehringer-Ingelheim GmbH; Eli Lilly and Company; Janssen Pharmaceuticals, Inc.; Novo Nordisk, Inc.; and Teva Pharmaceuticals USA, Inc.

ACKNOWLEDGMENTS

Editorial support for this supplement was provided by Gregory Scott, PharmD, RPh; Anna Wodlinger Jackson, PharmD, BCPS; and Angela Cimmino, PharmD.

REFERENCES

1. American Medical Association. Council on Ethical and Judicial Affairs Report B-I-90. Gender disparities in clinical decision-making. *JAMA*. 1991;266(4):559-562. http://www.ama-assn.org/resources/doc/code-medical-ethics/9122a.pdf. Accessed January 2, 2014.
2. Wizemann TM, Purdue ML, eds. *Exploring the Biological Contributions to Human Health: Does Sex Matter?* Washington, DC: National Academy Press, Institute of Medicine; 2001. http://www.nap.edu/openbook.php?isbn=0309072816. Accessed January 2, 2014.
3. Centers for Disease Control and Prevention. CDC WONDER (Wide-ranging Online Data for Epidemiologic Research). Mortality data for 1999-2009. http://wonder.cdc.gov/mortsql.html. Accessed January 2, 2014.
4. Agency for Healthcare Research and Quality. *Health Care Quality and Disparities in Women: Selected Findings from the 2010 National Healthcare Quality and Disparities Reports.* http://www.ahrq.gov/research/findings/nhqrdr/nhqrdr10/women.pdf. Published April 2011. Accessed January 2, 2014.
5. Jawaheer D, Messing S, Reed G, et al. Significance of sex in achieving sustained remission in the consortium of rheumatology researchers of North America cohort of rheumatoid arthritis patients. *Arthritis Care Res (Hoboken).* 2012;64(12):1811-1818.
6. Sokka T, Toloza S, Cutolo M, et al; QUEST-RA Group. Women, men, and rheumatoid arthritis: analyses of disease activity, disease characteristics, and treatments in the QUEST-RA study. *Arthritis Res Ther.* 2009;11(1):R7.
7. Elliott MN, Lehrman WG, Beckett MK, Goldstein E, Hambarsoomian K, Giordano LA. Gender differences in patients' perceptions of inpatient care. *Health Serv Res.* 2012;47(4):1482-1501.

Antiplatelet Therapy in Women With Acute Coronary Syndrome

JoAnne Foody, MD, FACC, FAHA

BACKGROUND

Heart disease remains the leading cause of death in the United States, yet many individuals are unaware of their coronary heart disease (CHD) risk. Up to 50% of men and 64% of women who die suddenly of CHD had no previous symptoms.[1,2] The risk of death is particularly high following a myocardial infarction (MI). In the first year following an MI, 26% of women over the age of 45 years die, rising to 47% within 5 years of a first MI. Since the 1980s, these death rates have declined slightly in most age groups. However, in women aged 35 to 44 years, the rate has been increasing annually by an average of 1.3%.[2] This rate increase in younger women is observed at a time when risk factors such as abdominal obesity, diabetes, and hypertension are also increasing in the population.[3] Despite improvements in knowledge and perception of cardiovascular disease (CVD), a recent survey conducted by the American Heart Association found that only 54% of women were aware that heart disease was the leading cause of death in women.[2]

The incidence of CVD remains higher in men than in women in all age categories; however, the gap between women and men narrows following menopause.[2,4] Differences in platelet biology and response to antiplatelet therapy have been hypothesized as possibly contributing to the gender differences observed.[4] Antiplatelet agents are included as key treatment options for acute coronary syndrome (ACS) in recent updates to non–ST elevation myocardial infarction (NSTEMI) and ST elevation myocardial infarction (STEMI) guidelines from the American College of Cardiology, the American Heart Association, and the Society for Cardiovascular Angiography and Interventions.[5-8] This article will focus on the use of antiplatelet agents for ACS and the differences between men and women in the efficacy and safety of antiplatelet agents. Recommendations for transition of care from the hospital to the primary care setting for women will also be discussed.

JoAnne Foody, MD, FACC, FAHA, Associate Professor, Harvard Medical School; Director of the Pollin Cardiovascular Wellness Program, Brigham and Women's Hospital; Director, Pollin Project for Cardiovascular Disease in Women, Boston, MA

DISCLOSURES

Dr. Foody discloses that she is on the advisory boards for Bristol-Myers Squibb Company; Janssen Pharmaceuticals, Inc.; Merck & Co.; and Sanofi US.

SUPPORT

This article is sponsored by PCEC and is supported by funding from AstraZeneca.

GENDER-RELATED DIFFERENCES IN ACUTE CORONARY SYNDROME

Acute coronary syndrome occurs as a result of atherosclerotic plaque rupture, platelet activation, and thrombus formation within a coronary artery.[9] Platelet aggregation is critical to the development of an occlusive thrombus and increased platelet reactivity has been associated with an elevated risk of acute coronary events.[9] Studies comparing platelet function in women and men have demonstrated that women have higher baseline platelet reactivity and aggregation.[10-12] This increase in platelet reactivity can result in an increased risk of ischemic events in some women.[13-15]

Inflammation

Inflammation can augment platelet response and further enhance platelet activation. One of the most widely studied markers of inflammation in cardiovascular risk has been high-sensitivity C-reactive protein (hs-CRP). Data in women and men show that hs-CRP levels are independently associated with risk for CHD, although the data are less consistent in women.[16-18] In a substudy of the Cardiovascular Health Study, hs-CRP levels did not add to the risk prediction in women at low and intermediate risk for CHD.[17] Current guideline recommendations do not include hs-CRP as a predictor of risk for CVD in women because there are no data to support an association between a reduction in hs-CRP and clinical outcomes.[19]

Female hormones

The role that female hormones play in CVD risk and platelet activity is not completely understood. Early evidence suggested a relationship between platelet aggregability and menstrual cycle phase.[20] In addition, megakaryocytes and platelets have been found to express both estrogen and

androgen receptors.[21] However, more recent data do not support a correlation with menstrual phase and hyperreactivity in platelets.[11,22]

The Women's Health Initiative was a large trial designed to study the clinical effects of hormone replacement therapy on CVD in women.[23] Given the observation that premenopausal women have a lower risk of heart disease than postmenopausal women, it was postulated that estrogen provides a cardioprotective effect. However, administering hormone therapy did not result in a lower risk of CVD in postmenopausal women.[23] With the complexity and multiple pathways involved in platelet activation and aggregation, there is a need for continued research in order to better understand the role of gender and hormones in thrombosis and risk of CVD.

CLINICAL PHARMACOLOGY OF ANTIPLATELET AGENTS AND USE IN WOMEN WITH ACUTE CORONARY SYNDROME

Aspirin

The benefits of antiplatelet agents in the prevention and treatment of ACS have been well established. Although an increasing variety of antiplatelet agents are used in the management of CVD, aspirin remains 1 of the most studied. The antiplatelet effects of aspirin occur as a result of irreversible inactivation of cyclooxygenase-1 (COX-1). This effect occurs at daily doses as low as 81 to 162 mg, whereas higher doses exert an additional effect on cyclooxygenase-2 (COX-2), resulting in inhibition of prostacyclin and its vasodilatory properties.[24,25] Recommended doses range from 81 to 325 mg daily, with lower doses (81 mg daily) preferred for most patients.[6,8,19]

Studies have found that platelet response to aspirin in women is similar to men, although overall platelet reactivity remains slightly higher in women, which is possibly due to higher baseline platelet reactivity.[11,12,26] Some clinical studies have found a benefit in women for primary prevention, while others have not.[27,28] The evidence suggests that the primary benefit in women is in prevention of ischemic strokes, but at the expense of an increased risk of bleeding.[27,29,30] Therefore, while the use of aspirin for primary prevention in women is controversial, aspirin is recommended for primary prevention in women 65 years or older who are at moderate or severe risk for CVD.[19,29,31] For secondary prevention, the benefits of aspirin are clear and aspirin is recommended for all women following ACS, including those who have undergone percutaneous coronary intervention (PCI).[5,6,8]

Adenosine diphosphate receptor antagonists

The oral antiplatelet agents used in conjunction with aspirin for the prevention of cardiovascular thrombotic events in patients with ACS are the adenosine diphosphate (ADP) receptor antagonists.[6-8] The thienopyridine class of ADP receptor antagonists includes clopidogrel and prasugrel; ticlopidine is no longer recommended. These agents exert their antiplatelet effect by irreversibly modifying the $P2Y_{12}$ receptor necessary for binding ADP and activating platelets. Ticagrelor is the newest ADP receptor antagonist and is in the cyclopentyltriazolopyrimidine class. In contrast to clopidogrel and prasugrel, ticagrelor reversibly inhibits the $P2Y_{12}$ receptor.[32,33] Despite the numerous studies evaluating the use of ADP receptor antagonists in the treatment of ACS, there is limited data that specifically examined their gender-related effects.

Clopidogrel

Clopidogrel has been available in the United States since 1997 and has been studied in a wide variety of thrombotic CVDs. It had been recommended as first-line therapy for secondary prevention in all patients with an MI.[31,34] Clopidogrel is a prodrug and requires a 2-step activation process that includes metabolism by hepatic cytochrome P450 enzymes (CYP2C19 and CYP3A4) to produce an active metabolite.[32,33] More than one-third of Europeans and over 40% of persons of African or Asian ancestry have genetic variants that lead to loss of function in their CYP2C19 isoform.[33,35] This loss of function leads to lower plasma concentrations of the active metabolite.[33] In addition, various drugs (ie, proton pump inhibitors) inhibit the CYP2C19 isoform and slow the metabolism of clopidogrel to its active form.[36] Lower levels of active metabolite can result in subtherapeutic antiplatelet effects and potentially worse clinical outcomes.[32,37-39] In 2010, the US Food and Drug Administration added a "boxed warning" to the clopidogrel label, suggesting genetic testing for patients prior to initiating clopidogrel therapy. The clinical and practical implementation of genetic testing has been questioned and remains a challenge.[35,38-40]

Of the 3 oral ADP antagonists available, the greatest amount of data in women is found in studies of clopidogrel. A study in healthy volunteers (23 male, 38 female) demonstrated less of a response in women to a single dose of clopidogrel 600 mg compared with men (platelet inhibition 40% in females vs 65% in males, $P = 0.04$) and a higher percentage of women meeting the definition of "nonresponders" compared with men (63% women vs 6% male, $P = 0.002$).[12] Platelet reactivity has also been assessed in postmenopausal women (n = 102) and men (n = 128) with known CVD and prior PCI on aspirin and clopidogrel therapy for at least 4 months.[41] In this prospective, observational study, women were found to have higher platelet aggregation than men.[41] The clinical implications of these trials were assessed in a meta-analysis that included 5 clopidogrel trials specifically

evaluating clinical outcomes in women compared with men.[42] Compared with placebo, clopidogrel reduced cardiovascular events in both women and men, although at the expense of a higher risk of major bleeding (**TABLE 1**). In women, the benefit was primarily due to a significant reduction in MI, with no significant effect on stroke or total death. In men, the risks of MI, stroke, and total death were significantly reduced with clopidogrel compared with placebo. Clopidogrel remains a class I recommendation for women and men following ACS or PCI with stent implantation.[6-8] Given the variable response due to genetic variability, genetic testing is suggested prior to initiating therapy in select patients, such as those at high risk for poor clinical outcomes.[6,7]

Prasugrel

Prasugrel is also in the thienopyridine class of ADP receptor antagonists but only requires 1 step for activation. The onset and extent of platelet inhibition is much more predictable and less variable with prasugrel than with clopidogrel.[43-46] This improved platelet inhibition compared to clopidogrel results in better clinical outcomes.[45,47] In the Trial to Assess Improvement in Therapeutic Outcomes by Optimizing Platelet Inhibition with Prasugrel–Thrombolysis in Myocardial Infarction 38 (TRITON–TIMI 38), patients undergoing PCI experienced fewer ischemic events with prasugrel than with clopidogrel (9.9% vs 12.1%, $P < 0.001$), but an increased risk of major bleeding with prasugrel (2.4% vs 1.1%, respectively; $P < 0.001$).[45,47] Currently, prasugrel is only recommended for use in patients with ACS who are to be managed with PCI.[48]

Data specific to women are limited to a subgroup analysis found within the original publication.[45] In women, prasugrel and clopidogrel were similarly effective in reducing the primary endpoint (death from cardiovascular causes, nonfatal MI, or nonfatal stroke). In men, prasugrel was found to be significantly more effective than clopidogrel. The efficacy of prasugrel was similar in women compared to men (**TABLE 2**). Consequently, current guidelines recommend prasugrel in patients undergoing PCI without any differentiation between men and women.[6-8]

Ticagrelor

Ticagrelor does not require activation to become biologically active and, similar to prasugrel, has a more rapid onset and predictable response compared with clopidogrel.[32,49,50] Ticagrelor binds reversibly to the $P2Y_{12}$ receptor and, due to its relatively short elimination half-life (7 hours for ticagrelor and 9 hours for the active metabolite), must be administered twice daily in contrast to clopidogrel and prasugrel, which require once daily dosing. The Study of Platelet Inhibition and Patient Outcomes (PLATO) compared ticagrelor to clopidogrel in patients with ACS (both STEMI and NSTEMI) who were medically or invasively managed (PCI/coronary artery bypass graft [CABG]).[49] Ticagrelor reduced cardiovascular outcomes (death from vascular causes, MI, or stroke) compared with clopidogrel (9.8% vs 11.7%, $P < 0.001$) and the rate of death from any cause was also reduced with ticagrelor. There was no difference in the overall rate of major bleeding, but non–CABG-related major bleeding was more common with ticagrelor (4.5% vs 3.8%; $P = .03$). Of note, the subgroup of North American patients did not demonstrate improvement with ticagrelor and further analyses attributed this outcome to the higher dose of aspirin used in the United States compared with outside the United States.[51] As a result, it is recommended that ticagrelor be administered with an aspirin dosage not exceeding 100 mg/day. Ticagrelor is currently indicated to reduce the rate of thrombotic cardiovascular events in patients with ACS.[52]

Several PLATO substudies have evaluated specific patient groups, but only 1 recent analysis reported outcomes in women.[53] This subset analysis of 5288 women and 13,336 men suggests that men and women had similar rates of the composite primary endpoint (cardiovascular death, MI, and stroke) and of all-cause mortality, but women had less overall major bleeding due to lower use of CABG surgery. In women with ACS, ticagrelor reduced ischemic events and mortality compared with clopidogrel without an increase in major bleeding (**TABLE 2**).[49,53] Current guidelines recommend the use of ticagrelor without any differentiation between men and women.[6-8]

Clinical considerations

The use of any antiplatelet agent involves balancing the benefits (reduction in CV morbidity and mortality) with the risks (bleeding and its complications).[54-56] Several studies have found that female gender is associated with increased risk of bleeding, particularly in those undergoing PCI (odds ratio, 1.3 to 2.6).[4,55,57-59] The reason for the increased risk in women is not completely understood; thus, close monitoring is recommended.

Given the increased risk of bleeding observed in women and the chance of diminished responsiveness to antiplatelet therapy, testing for platelet reactivity would seem to be of potential benefit.[60,61] Studies of platelet function testing to guide antiplatelet therapy, however, have not consistently demonstrated this benefit clinically.[44,61,62] Consequently, current guidelines do not recommend that platelet function testing prior to ADP receptor antagonist therapy be performed.[6,7]

In summary, the use of aspirin (81 mg/day preferred maintenance dose) for secondary prevention of CVD is recommended in women, whereas aspirin is only recommended in select female patients for primary preven-

TABLE 1 Results of a meta-analysis of clopidogrel in women and men[42]

Population	Outcomes in women and men
Various populations including ACS and PCI (N = 79,613; women: n = 23,533)	**CV events** Women: 11% clopidogrel vs 11.8% placebo (OR, 0.93; 95% CI: 0.86 to 1.01) Men: 7.8% clopidogrel vs 9% placebo (OR, 0.84; 95% CI: 0.78 to 0.91) **MI** Women: 2.9% clopidogrel vs 3.6% placebo (OR, 0.81; 95% CI: 0.70 to 0.93) Men: 2.8% clopidogrel vs 3.4% placebo (OR, 0.83; 95% CI: 0.76 to 0.92) **Stroke** Women: 1.6% clopidogrel vs 1.9% placebo (OR, 0.91; 95% CI: 0.69 to 1.21) Men: NR (OR, 0.83; 95% CI: 0.71 to 0.96) **Total death** Women: 8.7% clopidogrel vs 8.8% placebo (OR, 0.99; 95% CI: 0.90 to 1.08) Men: 5.4% clopidogrel vs 6.0% placebo (OR, 0.91; 95% CI: 0.84 to 0.97) **Major bleeding** Women: 1.7% clopidogrel vs 1.2% placebo (OR, 1.43; 95% CI: 1.15 to 1.79) Men: 1.3% clopidogrel vs 1.1% placebo (OR, 1.22; 95% CI: 1.05 to 1.42)

Abbreviations: ACS, acute coronary syndrome; CI, confidence interval; CV, cardiovascular; MI, myocardial infarction; NR, not reported; OR, odds ratio; PCI, percutaneous coronary intervention.

TABLE 2 Outcomes in women and men with prasugrel and ticagrelor

Study	Population	Outcomes
TRITON-TIMI 38[45] Prasugrel 60 mg x 1, then 10 mg QD or Clopidogrel 300 mg x 1, then 75 mg QD for 6-15 months	Moderate- to high-risk ACS undergoing PCI N = 13,608 Women: n = 3523; Men: n = 10,085	**CV death, nonfatal MI, or nonfatal stroke** Women: 11.0% prasugrel vs 12.6% clopidogrel (risk reduction, 12%; 95% CI crosses 1.00) Men: 9.5% prasugrel vs 11.9% clopidogrel (risk reduction, 21%; 95% CI does not cross 1.00)
PLATO[49,53] Ticagrelor 180 mg x 1, then 90 mg BID or Clopidogrel 300-600 mg x 1, then 75 mg QD for 12 months	ACS with or without PCI N = 18,624 Women: n = 5288 Men: n = 13,336	**CV death, MI, or stroke** Women: 11.2% ticagrelor vs 13.2% clopidogrel (HR, 0.88; 95% CI: 0.74 to 1.06) Men: 9.4% ticagrelor vs 11.1% clopidogrel (HR, 0.87; 95% CI: 0.77 to 0.98) **All-cause mortality** Women: 5.8% ticagrelor vs 6.8% clopidogrel (HR, 0.92; 95% CI: 0.71 to 1.19) Men: 4.0% ticagrelor vs 5.7% clopidogrel (HR, 0.82; 95% CI: 0.68 to 0.99) **Major bleeding** Women: 10.7% ticagrelor vs 10.6% clopidogrel (HR, 1.00; 95% CI: 0.82 to 1.22) Men: 12.0% ticagrelor vs 11.5% clopidogrel (HR, 1.10; 95% CI: 0.98 to 1.24)

Abbreviations: ACS, acute coronary syndrome; BID, twice daily; CI, confidence interval; CV, cardiovascular; HR, hazard ratio; MI, myocardial infarction; PCI, percutaneous coronary intervention; QD, once daily.

tion.[5,6,8,19,29,31] Despite the limited analyses comparing results in women vs men, the use of an ADP receptor antagonist in addition to aspirin is recommended for all patients following an ACS, particularly patients who undergo PCI with stent implantation.[5-8] Data suggest that clopidogrel therapy may be somewhat less effective and somewhat less safe in women than in men, although the mechanisms underlying these differences are unclear.[12,41]

TRANSITION FROM THE HOSPITAL TO PRIMARY CARE: IMPORTANT CONSIDERATIONS FOR PRIMARY CARE PHYSICIANS

Postdischarge communication and care for the patient who has been hospitalized for ACS is critical to preventing readmissions and complications.[8,63-65] All patients being discharged following ACS should be referred to cardiac rehabilitation; women, however, are less likely to receive referrals or enroll in cardiac rehabilitation.[8,66] Another important aspect of postdischarge care is medication reconciliation, as medication changes often occur during hospitalizations.[64] Assessment of adherence is critical since recent evidence suggests that patients often discontinue drug therapy following discharge from the hospital.[64,67,68] This has important implications for the occurrence of subsequent events, because discontinuation of antiplatelet agents is associated with an increased risk of stent thrombosis.[68-70] Similarly, once stabilized on an effective antiplatelet regimen during the hospital stay, the patient should continue on the same antiplatelet regimen as an outpatient unless a change is clinically indicated. Discontinuing the antiplatelet regimen (eg, for issues related to medication costs) may place the patient at increased risk of a recurrent event.[71] In addition to medication adherence, coordination of care with the patient's health care team to provide comprehensive cardiovascular risk reduction, including weight management, smoking cessation (avoidance of secondhand smoke), blood pressure control, healthy lipid levels, and management of diabetes, is important.[8] This is another opportunity for the primary care provider to advise the patient on appropriate care following ACS as part of a comprehensive posthospitalization plan of care in collaboration with other health care providers.[8]

CONCLUSION

Differences in platelet reactivity between men and women exist and limited data suggest that response to antiplatelet therapy may be different in women compared with men. The exact mechanism and influence of genetic determinants and hormones on CVD in women has not been fully elucidated. The use of genetic testing and platelet reactivity testing may be beneficial in some patients, but their roles in routine clinical practice remain controversial. As primary prevention for cardiovascular events, aspirin has not consistently demonstrated benefit in women and is only recommended in select patients. For secondary prevention, women and men achieve similar outcomes with antiplatelet therapy. Assessing medication compliance, performing comprehensive risk reduction, and referring to cardiac rehabilitation are proven to be beneficial for all women with CVD and should continue to be promoted by primary care physicians. ●

REFERENCES

1. Murphy SL, Xu J, Kochanek KD; Division of Vital Statistics. Deaths: preliminary data for 2010. Natl Vital Stat Rep. 2012;60(4):1-52. http://www.cdc.gov/nchs/data/nvsr/nvsr60/nvsr60_04.pdf. Published 2012. Accessed January 2, 2014.
2. Go AS, Mozaffarian D, Roger VL, et al; American Heart Association Statistics Committee and Stroke Statistics Subcommittee. Heart disease and stroke statistics—2013 update: a report from the American Heart Association [published corrections appear in *Circulation*. 2013;127(23):e841; *Circulation*. 2013;127(1):doi:10.1161/CIR.0b013e31828124ad]. *Circulation*. 2013;127(1):e6-e245.
3. Ford ES, Capewell S. Coronary heart disease mortality among young adults in the U.S. from 1980 through 2002: concealed leveling of mortality rates. *J Am Coll Cardiol*. 2007;50(22):2128-2132.
4. Wang TY, Angiolillo DJ, Cushman M, et al. Platelet biology and response to antiplatelet therapy in women: implications for the development and use of antiplatelet pharmacotherapies for cardiovascular disease. *J Am Coll Cardiol*. 2012;59(10):891-900.
5. Smith SC, Jr., Benjamin EJ, Bonow RO, et al; World Heart Federation and the Preventive Cardiovascular Nurses Association. AHA/ACCF Secondary Prevention and Risk Reduction Therapy for Patients With Coronary and other Atherosclerotic Vascular Disease: 2011 update: a guideline from the American Heart Association and American College of Cardiology Foundation. *Circulation*. 2011;124(22):2458-2473.
6. Jneid H, Anderson JL, Wright RS, et al; 2012 Writing Committee Members; American College of Cardiology Foundation; American Heart Association Task Force on Practice Guidelines. 2012 ACCF/AHA focused update of the guideline for the management of patients with unstable angina/Non-ST-elevation myocardial infarction (updating the 2007 guideline and replacing the 2011 focused update): a report of the American College of Cardiology Foundation/American Heart Association Task Force on practice guidelines. *Circulation*. 2012;126(7):875-910.
7. Levine GN, Bates ER, Blankenship JC, et al. 2011 ACCF/AHA/SCAI Guideline for Percutaneous Coronary Intervention: a report of the American College of Cardiology Foundation/American Heart Association Task Force on Practice Guidelines and the Society for Cardiovascular Angiography and Interventions [published correction appears in *Circulation*. 2012;125(8):e412]. *Circulation*. 2011;124(23):e574-e651.
8. O'Gara PT, Kushner FG, Ascheim DD, et al; American College of Cardiology Foundation/American Heart Association Task Force on Practice Guidelines. 2013 ACCF/AHA guideline for the management of ST-elevation myocardial infarction: a report of the American College of Cardiology Foundation/American Heart Association Task Force on Practice Guidelines. *Circulation*. 2013;127(4):e362-e425.
9. Arbab-Zadeh A, Nakano M, Virmani R, Fuster V. Acute coronary events. *Circulation*. 2012;125(9):1147-1156.
10. Kurrelmeyer K, Becker L, Becker D, Yanek L, Goldschmidt-Clermont P, Bray PF. Platelet hyperreactivity in women from families with premature atherosclerosis. *J Am Med Womens Assoc*. 2003;58(4):272-277.
11. Becker DM, Segal J, Vaidya D, et al. Sex differences in platelet reactivity and response to low-dose aspirin therapy. *JAMA*. 2006;295(12):1420-1427.
12. Hobson AR, Qureshi Z, Banks P, Curzen N. Gender and responses to aspirin and clopidogrel: insights using short thrombelastography. *Cardiovasc Ther*. 2009;27(4):246-252.
13. Snoep JD, Roest M, Barendrecht AD, De Groot PG, Rosendaal FR, Van Der Bom JG. High platelet reactivity is associated with myocardial infarction in premenopausal women: a population-based case-control study. *J Thromb Haemost*. 2010;8(5):906-913.
14. Gurbel PA, Bliden KP, Cohen E, et al. Race and sex differences in thrombogenicity: risk of ischemic events following coronary stenting. *Blood Coagul Fibrinolysis*. 2008;19(4):268-275.
15. Appelman Y, de Winter RJ. Female platelets are hard to control. *Neth Heart J*. 2011;19(11):449-450.
16. Ridker PM, Hennekens CH, Buring JE, Rifai N. C-reactive protein and other markers of inflammation in the prediction of cardiovascular disease in women. *N Engl J Med*. 2000;342(12):836-843.
17. Cushman M, Arnold AM, Psaty BM, et al. C-reactive protein and the 10-year incidence of coronary heart disease in older men and women: the cardiovascular health study. *Circulation*. 2005;112(1):25-31.
18. Buckley DI, Fu R, Freeman M, Rogers K, Helfand M. C-reactive protein as a risk factor for coronary heart disease: a systematic review and meta-analyses for the U.S. Preventive Services Task Force. *Ann Intern Med*. 2009;151(7):483-495.
19. Mosca L, Benjamin EJ, Berra K, et al. Effectiveness-based guidelines for the prevention of cardiovascular disease in women—2011 update: a guideline from the American Heart Association [published corrections appear in *Circulation*. 2011;123(22):e624; *Circulation*. 2011;124:e427]. *Circulation*. 2011;123(11):1243-1262.
20. Tarantino MD, Kunicki TJ, Nugent DJ. The estrogen receptor is present in human megakaryocytes. *Ann N Y Acad Sci*. 1994;714:293-296.
21. Khetawat G, Faraday N, Nealen ML, et al. Human megakaryocytes and platelets contain the estrogen receptor beta and androgen receptor (AR): testosterone regulates AR expression. *Blood*. 2000;95(7):2289-2296.
22. Yee DL, Sun CW, Bergeron AL, Dong JF, Bray PF. Aggregometry detects platelet hyperreactivity in healthy individuals. *Blood*. 2005;106(8):2723-2729.
23. Rossouw JE, Anderson GL, Prentice RL, et al; Writing Group for the Women's Health Initiative Investigators. Risks and benefits of estrogen plus progestin in healthy post-

menopausal women: principal results from the Women's Health Initiative randomized controlled trial. *JAMA*. 2002;288(3):321-333.
24. Fuster V, Sweeny JM. Aspirin: a historical and contemporary therapeutic overview. *Circulation*. 2011;123(7):768-778.
25. Patrono C, Andreotti F, Arnesen H, et al. Antiplatelet agents for the treatment and prevention of atherothrombosis. *Eur Heart J*. 2011;32(23):2922-2932.
26. Zuern CS, Lindemann S, Gawaz M. Platelet function and response to aspirin: gender-specific features and implications for female thrombotic risk and management. *Semin Thromb Hemost*. 2009;35(3):295-306.
27. Ridker PM, Cook NR, Lee IM, et al. A randomized trial of low-dose aspirin in the primary prevention of cardiovascular disease in women. *N Engl J Med*. 2005;352(13):1293-1304.
28. Baigent C, Blackwell L, Collins R, et al; Antithrombotic Trialists' (ATT) Collaboration. Aspirin in the primary and secondary prevention of vascular disease: collaborative meta-analysis of individual participant data from randomised trials. *Lancet*. 2009;373(9678):1849-1860.
29. Wolff T, Miller T, Ko S. Aspirin for the primary prevention of cardiovascular events: an update of the evidence for the U.S. Preventive Services Task Force. *Ann Intern Med*. 2009;150(6):405-410.
30. Berger JS, Roncaglioni MC, Avanzini F, Pangrazzi I, Tognoni G, Brown DL. Aspirin for the primary prevention of cardiovascular events in women and men: a sex-specific meta-analysis of randomized controlled trials. *JAMA*. 2006;295(3):306-313.
31. Lansky AJ, Hochman JS, Ward PA, et al; American College of Cardiology Foundation; American Heart Association. Percutaneous coronary intervention and adjunctive pharmacotherapy in women: a statement for healthcare professionals from the American Heart Association. *Circulation*. 2005;111(7):940-953.
32. Oh EY, Abraham T, Saad N, Rapp JH, Vastey FL, Balmir E. A comprehensive comparative review of adenosine diphosphate receptor antagonists. *Expert Opin Pharmacother*. 2012;13(2):175-191.
33. Wallentin L. P2Y(12) inhibitors: differences in properties and mechanisms of action and potential consequences for clinical use. *Eur Heart J*. 2009;30(16):1964-1977.
34. Antman EM, Hand M, Armstrong PW, et al. 2007 Focused Update of the ACC/AHA 2004 Guidelines for the Management of Patients With ST-Elevation Myocardial Infarction: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines: developed in collaboration with the Canadian Cardiovascular Society endorsed by the American Academy of Family Physicians: 2007 Writing Group to Review New Evidence and Update the ACC/AHA 2004 Guidelines for the Management of Patients With ST-Elevation Myocardial Infarction, Writing on Behalf of the 2004 Writing Committee [published correction appears in *Circulation*. 2008;117(6):e162]. *Circulation*. 2008;117(2):296-329.
35. Damani SB, Topol EJ. The case for routine genotyping in dual-antiplatelet therapy. *J Am Coll Cardiol*. 2010;56(2):109-111.
36. Abraham NS, Hlatky MA, Antman EM, et al; ACCF/ACG/AHA. ACCF/ACG/AHA 2010 Expert Consensus Document on the concomitant use of proton pump inhibitors and thienopyridines: a focused update of the ACCF/ACG/AHA 2008 expert consensus document on reducing the gastrointestinal risks of antiplatelet therapy and NSAID use: a report of the American College of Cardiology Foundation Task Force on Expert Consensus Documents. *Circulation*. 2010;122(24):2619-2633.
37. Erlinge D, Varenhorst C, Braun OO, et al. Patients with poor responsiveness to thienopyridine treatment or with diabetes have lower levels of circulating active metabolite, but their platelets respond normally to active metabolite added ex vivo. *J Am Coll Cardiol*. 2008;52(24):1968-1977.
38. Cattaneo M. Response variability to clopidogrel: is tailored treatment, based on laboratory testing, the right solution? *J Thromb Haemost*. 2012;10(3):327-336.
39. Fontana P, Cattaneo M, Combescure C, Reny JL. Tailored thienopyridine therapy: no urgency for CYP2C19 genotyping. *J Am Heart Assoc*. 2013;2(2):e000131.
40. Plavix [package insert]. Bridgewater, NJ: Bristol-Myers Squibb/Sanofi Pharmaceuticals Partnership; 2013.
41. Bobbert P, Stellbaum C, Steffens D, et al. Postmenopausal women have an increased maximal platelet reactivity compared to men despite dual antiplatelet therapy. *Blood Coagul Fibrinolysis*. 2012;23(8):723-728.
42. Berger JS, Bhatt DL, Cannon CP, et al. The relative efficacy and safety of clopidogrel in women and men a sex-specific collaborative meta-analysis. *J Am Coll Cardiol*. 2009;54(21):1935-1945.
43. Farid NA, Kurihara A, Wrighton SA. Metabolism and disposition of the thienopyridine antiplatelet drugs ticlopidine, clopidogrel, and prasugrel in humans [published correction appears in *J Clin Pharmacol*. 2010;50(2):126-42]. *J Clin Pharmacol*. 2010;50(2):126-142.
44. Cattaneo M. New P2Y(12) inhibitors. *Circulation*. 2010;121(1):171-179.
45. Wiviott SD, Braunwald E, McCabe CH, et al; TRITON-TIMI 38 Investigators. Prasugrel versus clopidogrel in patients with acute coronary syndromes. *N Engl J Med*. 2007;357(20):2001-2015.
46. Wallentin L, Varenhorst C, James S, et al. Prasugrel achieves greater and faster P2Y12receptor-mediated platelet inhibition than clopidogrel due to more efficient generation of its active metabolite in aspirin-treated patients with coronary artery disease. *Eur Heart J*. 2008;29(1):21-30.
47. Michelson AD, Frelinger AL III, Braunwald E, et al; TRITON-TIMI 38 Investigators. Pharmacodynamic assessment of platelet inhibition by prasugrel vs. clopidogrel in the TRITON-TIMI 38 trial. *Eur Heart J*. 2009;30(14):1753-1763.
48. Effient [package insert]. Indianapolis, IN: Eli Lilly and Company; 2013.
49. Wallentin L, Becker RC, Budaj A, et al; PLATO Investigators. Ticagrelor versus clopidogrel in patients with acute coronary syndromes. *N Engl J Med*. 2009;361(11):1045-1057.
50. Gurbel PA, Bliden KP, Butler K, et al. Randomized double-blind assessment of the ONSET and OFFSET of the antiplatelet effects of ticagrelor versus clopidogrel in patients with stable coronary artery disease: the ONSET/OFFSET study. *Circulation*. 2009;120(25):2577-2585.
51. Mahaffey KW, Wojdyla DM, Carroll K, et al; PLATO Investigators. Ticagrelor compared with clopidogrel by geographic region in the Platelet Inhibition and Patient Outcomes (PLATO) trial. *Circulation*. 2011;124(5):544-554.
52. Brilinta [package insert]. Wilmington, DE: AstraZeneca; 2013.
53. Husted S, James S, Becker R, et al. Ticagrelor versus clopidogrel in women with acute coronary syndromes: a substudy from the prospective randomized platelet inhibition and patient outcomes (PLATO) trial. *J Am Coll Cardiol*. 2012;59(13s1):E507. http://content.onlinejacc.org/article.aspx?articleid=1204586. Published March 2012. Accessed January 2, 2014.
54. Eikelboom JW, Mehta SR, Anand SS, Xie C, Fox KA, Yusuf S. Adverse impact of bleeding on prognosis in patients with acute coronary syndromes. *Circulation*. 2006;114(8):774-782.
55. Subherwal S, Bach RG, Chen AY, et al. Baseline risk of major bleeding in non-ST-segment-elevation myocardial infarction: the CRUSADE (Can Rapid risk stratification of Unstable angina patients Suppress ADverse outcomes with Early implementation of the ACC/AHA Guidelines) Bleeding Score. *Circulation*. 2009;119(14):1873-1882.
56. Manoukian SV, Feit F, Mehran R et al. Impact of major bleeding on 30-day mortality and clinical outcomes in patients with acute coronary syndromes: an analysis from the ACUITY Trial. *J Am Coll Cardiol*. 2007;49(12):1362-1368.
57. Piper WD, Malenka DJ, Ryan TJ Jr, et al; Northern New England Cardiovascular Disease Study Group. Predicting vascular complications in percutaneous coronary interventions. *Am Heart J*. 2003;145(6):1022-1029.
58. Ahmed B, Piper WD, Malenka D, et al. Significantly improved vascular complications among women undergoing percutaneous coronary intervention: a report from the Northern New England Percutaneous Coronary Intervention Registry. *Circ Cardiovasc Interv*. 2009;2(5):423-429.
59. Moscucci M, Fox KA, Cannon CP, et al. Predictors of major bleeding in acute coronary syndromes: the Global Registry of Acute Coronary Events (GRACE). *Eur Heart J*. 2003;24(20):1815-1823.
60. Bonello L, Tantry US, Marcucci R, et al; Working Group on High On-Treatment Platelet Reactivity. Consensus and future directions on the definition of high on-treatment platelet reactivity to adenosine diphosphate. *J Am Coll Cardiol*. 2010;56(12):919-933.
61. Price MJ. Monitoring platelet function to reduce the risk of ischemic and bleeding complications. *Am J Cardiol*. 2009;103(3 Suppl):35A-39A.
62. Collet JP, Cuisset T, Rangé G, et al; ARCTIC Investigators. Bedside monitoring to adjust antiplatelet therapy for coronary stenting. *N Engl J Med*. 2012;367(22):2100-2109.
63. Kesavan S, Kelay T, Collins RE, et al. Clinical information transfer and data capture in the acute myocardial infarction pathway: an observational study. *J Eval Clin Pract*. 2013;19(5):805-811.
64. Villanueva T. Transitioning the patient with acute coronary syndrome from inpatient to primary care. *J Hosp Med*. 2010;5(Suppl 4):S8-14.
65. Kripalani S, LeFevre F, Phillips CO, Williams MV, Basaviah P, Baker DW. Deficits in communication and information transfer between hospital-based and primary care physicians: implications for patient safety and continuity of care. *JAMA*. 2007;297(8):831-841.
66. Balady GJ, Ades PA, Bittner VA, et al; American Heart Association Science Advisory and Coordinating Committee. Referral, enrollment, and delivery of cardiac rehabilitation/secondary prevention programs at clinical centers and beyond: a presidential advisory from the American Heart Association. *Circulation*. 2011;124(25):2951-2960.
67. Melloni C, Alexander KP, Ou FS, et al. Predictors of early discontinuation of evidence-based medicine after acute coronary syndrome. *Am J Cardiol*. 2009;104(2):175-181.
68. Ferreira-González I, Marsal JR, Ribera A, et al. Background, incidence, and predictors of antiplatelet therapy discontinuation during the first year after drug-eluting stent implantation. *Circulation*. 2010;122(10):1017-1025.
69. Ho PM, Tsai TT, Maddox TM, et al. Delays in filling clopidogrel prescription after hospital discharge and adverse outcomes after drug-eluting stent implantation: implications for transitions of care. *Circ Cardiovasc Qual Outcomes*. 2010;3(3):261-266.
70. Grines CL, Bonow RO, Casey DE Jr, et al; American Heart Association; American College of Cardiology; Society for Cardiovascular Angiography and Interventions; American College of Surgeons; American Dental Association; American College of Physicians. Prevention of premature discontinuation of dual antiplatelet therapy in patients with coronary artery stents: a science advisory from the American Heart Association, American College of Cardiology, Society for Cardiovascular Angiography and Interventions, American College of Surgeons, and American Dental Association, with representation from the American College of Physicians. *Circulation*. 2007;115(6):813-818.
71. Kohli P, Wallentin L, Reyes E, et al. Reduction in first and recurrent cardiovascular events with ticagrelor compared with clopidogrel in the PLATO Study. *Circulation*. 2013;127(6):673-680.

Coronary Heart Disease in Women

Michael Cobble, MD, FAAFP, FNLA

Although cardiovascular disease is still the leading cause of death in both women and men in the United States, the mortality rates due to cardiovascular disease declined and then leveled off from 1980 to 2009.[1-3] From 2000 to 2009, the crude mortality rate for ischemic heart disease–related deaths in women declined from 177.6 to 113.3 per 100,000 population, whereas in men, the rate declined from 188.7 to 138.7 deaths per 100,000 population.[3] Further evidence also suggests that women experience a smaller burden due to coronary heart disease (CHD) than men. The overall prevalence of CHD is estimated to be 5.1% in women compared with 7.9% in men.[1] Moreover, the lifetime risk of developing CHD after 40 years of age is 32% in women and 49% in men; in addition, the incidence of CHD in women lags behind men by 10 years for CHD overall and by 20 years for myocardial infarction (MI) and sudden death.[1]

Other evidence suggests that women carry a heavier cardiovascular burden due to CHD because women generally face a worse prognosis than men following a primary event.[1,4] For example, after a first MI, 26% of women and 19% of men aged 45 years or older die within 1 year and 47% and 36%, respectively, die within 5 years. In addition, within 5 years after a first MI, 18% of women and 8% of men aged 45 to 64 years develop heart failure.[1] In patients with known CHD and diabetes, women are more likely than men to be symptomatic, including angina, atypical angina, or an angina equivalent.[5]

The reasons for the differences in CHD burden between women and men are not clear, although greater adverse coronary reactivity, microvascular dysfunction, and plaque erosion and distal microembolization in women have been suggested.[6] In men, 80% of coronary thrombi tend to occur because of plaque rupture. In women, 20% to 40% of coronary thrombi occur on an intact plaque with superficial atherointimal erosion, and women generally have less obstructive CHD.[7-9] It is also likely that patient and provider awareness impact the burden of CHD in women. While awareness by women of the contribution of major risk factors to CHD has increased over the past 15 years, women at highest risk are the least aware.[10-12] In addition, women generally receive fewer preventive services for CHD and less treatment intensification than do men.[13,14] Significant knowledge deficits among health care providers are a likely contributing factor.[15]

Understanding the differences between women and men regarding CHD has important clinical management implications. This review is similar to a review of CHD in men published in a supplement to *The Journal of Family Practice* in June 2012[16]; however, this review emphasizes the differences between women and men regarding key risk factors, patient assessment, and treatment for primary prevention of CHD.

RISK FACTORS

Traditional risk factors

Common risk factors for CHD, such as hypertension, dyslipidemia, abdominal obesity, diabetes mellitus, and smoking, are highly prevalent in women, with many having a greater impact and/or prevalence than in men.[6,17-19] With respect to dyslipidemia, hypertriglyceridemia is especially important and appears to confer a greater risk in women compared with men.[20,21] Furthermore, the ratio of triglyceride to high-density lipoprotein cholesterol (HDL-C) is a strong, independent predictor of all-cause mortality and cardiovascular events in women. One investigation showed that women in the highest triglyceride/HDL-C ratio quartile (3.66 to 18.4) had nearly twice as many cardiovascular events as women in the

Michael Cobble, MD, FAAFP, FNLA, Diplomate, American Board of Clinical Lipidology; Certified Hypertension Specialist, private practice, Sandy, UT; Adjunct Faculty, University of Utah School of Medicine, Salt Lake City, UT

DISCLOSURES

Dr. Cobble discloses that he receives a salary from Atherotech Cardiometabolic Lab. He discloses that he is on the advisory boards for Amarin Corporation; AstraZeneca; Bristol-Myers Squibb Company; Eli Lilly and Company/Kowa Pharmaceuticals America, Inc.; Genentech, Inc., a member of the Roche group; Novo Nordisk, Inc.; and Vivus, Inc. He is on the speakers' bureaus for Amarin Corporation; AstraZeneca; Bristol-Myers Squibb; Eli Lilly and Company/Kowa Pharmaceuticals America, Inc.; and Vivus, Inc.

SUPPORT

This article is sponsored by PCEC and is supported by funding from AstraZeneca.

lowest triglyceride/HDL-C ratio quartile (0.35 to <1.4) over 6 years of follow-up.[10] Smoking is also especially consequential in women, conferring a 25% increase in CHD risk compared with male smokers.[22] Since hypertriglyceridemia and tobacco use confer a higher risk in women, targeting them with lifestyle management and patient support is essential.

Estimates from the Second National Health and Nutrition Examination Survey (NHANES II) baseline data and 17-year mortality follow-up data indicate that 64% of CHD-related deaths in women could be avoided by eliminating 3 major risk factors: total cholesterol ≥240 mg/dL, hypertension, and smoking.[23] Unfortunately, multiple investigations show that many adults do not achieve low-density lipoprotein cholesterol (LDL-C), triglyceride, or blood pressure (BP) targets and that approximately 20% of adults smoke cigarettes.[24-29]

The importance of addressing these unmet goals cannot be overstated, because a greater cardiac risk factor burden in middle age is associated with poorer quality of life, higher incidence of cardiovascular events, and higher medical costs in older age.[1,30] However, about half of patients with CHD are not diagnosed until symptoms become apparent—typically after middle age.[31] For these reasons, it is of paramount importance that assessment and appropriate interventions targeting risk factors for CHD in women, including psychosocial factors, begin in early adulthood.

Psychosocial factors

Psychosocial factors play an important role in a woman's risk of future CHD-related events. The factors listed in **TABLE 1** can increase or reduce the risk for CHD in women.[32-38] The combination of several common psychosocial factors (depression, perceived stress, and life events) confers a risk for MI at a rate comparable to that of current and former smoking.[19] Importantly, many psychosocial risk factors in women confer higher risk than in men.[19]

CLINICAL ASSESSMENT

Despite the large number of possible risk factors, the assessment of CHD risk can generally be kept simple to facilitate consistent application in clinical practice. The assessment should include a family, social, and personal medical history, and a physical examination. It is important to keep in mind that the presentation of CHD in women may be more subtle than in men. Fatigue is the most common prodromal symptom of an acute MI in women. Other common symptoms include sleep disturbance, anxiety, shortness of breath, and frequent indigestion; only one-third of women report any chest discomfort or pain during the prodromal period.[39] Women with the following characteristics are more likely to experience a higher number and severity of prodromal symptoms: non-Caucasian, younger age, obese, personal history of cardiovascular disease, and smoking history.[40] Initial laboratory evaluation should include the lipid profile and glycated hemoglobin (HbA_{1c}). Beyond the triglyceride level, the importance of apolipoprotein (apo) levels to cardiovascular risk continues to emerge.[41] The apo B concentration represents the sum of the atherogenic lipoprotein particles found on non–HDL-C, whereas the apo A concentration represents the sum of the antiatherogenic lipoprotein particles found on HDL-C. The apo B and/or non–HDL-C levels in particular may be more useful than LDL-C to assess residual cardiovascular risk and determine the need for medication adjustments, once the LDL-C target is attained.[41] HDL-C <50 mg/dL is a risk factor for cardiometabolic syndrome in women and HDL-C <40 mg/dL is a cardiovascular risk factor, based on National Cholesterol Education Program Adult Treatment Panel III guidelines.[42] HDL-C is not the target of therapy, but rather a predictor of risk. For global risk management, the best evidence supports controlling BP and LDL-C, tobacco cessation, and lifestyle management, which includes diet, exercise, and stress support therapies. The Framingham Risk Score (www.framinghamheartstudy.org/risk/gencardio.html) and the Reynolds Risk Score (www.reynoldsriskscore.org) can be used to estimate the 10-year risk of CHD.

TREATMENT

The principal treatment goal in a woman (or man) with 1 or more modifiable risk factors for CHD is to prevent an initial or primary cardiovascular event. The strategies to achieve this goal in women are the same as in men, as there are few data suggesting a gender-related difference in response and benefit. Lifestyle changes consisting of a Dietary Approaches to Stop Hypertension (DASH)-like diet, smoking cessation, regular physical activity, and weight management are cornerstones of overall management.[43] In addition, increasing adherence to a Mediterranean style diet, particularly if supplemented with olive oil or nuts, is inversely related to the risk of cardiovascular disease in women.[44-46]

Lipids

The benefits of preventing a first episode of MI or stroke by lowering LDL-C have been clearly demonstrated in numerous clinical trials.[47-50] The cardiovascular benefits associated with lowering LDL-C have been demonstrated in individuals with large as well as modest elevations of or even normal LDL-C. Results of the Justification for the Use of Statins in Prevention: An Intervention Trial Evaluating Rosuvastatin (JUPITER) (N = 17,802) showed that the rates of the pri-

TABLE 1 Association of psychosocial factors with coronary heart disease risk in women[32-38]

Increased risk for CHD in women	Unclear association with CHD risk in women	Reduced risk for CHD in women
• Depression	• Anxiety	• Presence of a spouse/partner
• Anger suppression	• Hostility	• Optimism
• Stress	• Large social network	• Positive psychological attributes
–High demand and low control at work		
–Experienced at both home and work		
• Low social support/interaction		
• Frequent loneliness		
• Health self-rated as fair/poor		

Abbreviation: CHD, coronary heart disease.

mary endpoint (MI, stroke, arterial revascularization, hospitalization for unstable angina, or cardiovascular death) were significantly lower in persons with LDL-C <130 mg/dL and high-sensitivity C-reactive protein ≥2 mg/L at baseline who were treated with rosuvastatin compared with placebo (0.77 vs 1.36 events per 100 person-years of follow-up; $P < .00001$).[50] The benefits of progressively lowering the LDL-C level have been demonstrated in 2 meta-analyses.[51,52] For example, the Cholesterol Treatment Trialists' Collaboration (N = 169,138) found that all-cause mortality was reduced by 10% for every 39 mg/dL reduction in LDL-C ($P < .0001$). This was largely due to a 20% reduction in deaths due to CHD ($P < .0001$) and an 11% reduction in deaths due to other cardiac causes ($P = .002$).[51] Additional clinical trials provide further support for the cardiovascular benefits of intensive high-dose statin therapy.[53] The Study of Coronary Atheroma by Intravascular Ultrasound: Effect of Rosuvastatin versus Atorvastatin (SATURN) demonstrated reductions in coronary atheroma volume of 1.22% with rosuvastatin 40 mg/day and 0.99% with atorvastatin 80 mg/day over 104 weeks.[54] The long-term benefits of statin therapy have been demonstrated as well, with benefits sustained after 11 years.[55-57]

Although high-dose statin therapy has demonstrated significant cardiovascular risk reduction, there is an increased risk of myotoxicity and hepatotoxicity. In addition, a possible association with new-onset diabetes has been raised observationally. In the JUPITER trial, patients treated with a statin experienced a 25% higher incidence of new-onset diabetes compared with those receiving placebo.[50] Significant increases in HbA_{1c} and fasting plasma insulin levels have also been observed with various doses of atorvastatin, compared with placebo, after 8 weeks (all $P < .01$).[58] However, a meta-analysis of 6 major statin clinical trials (N = 57,593) showed no significant increase in the risk of diabetes with statin therapy compared with placebo ($P = .38$).[59] Further analysis of 5 major statin trials involving 32,752 patients without diabetes at baseline demonstrated a 12% higher risk of developing diabetes mellitus with intensive- versus moderate-dose statin therapy.[60] Based on these results, the investigators determined that 1 additional case of diabetes mellitus would result from treating 498 patients with intensive-dose statin therapy for 1 year, whereas 1 additional case of a cardiovascular event would be avoided by treating only 155 patients for 1 year. These findings support the greater cardiovascular benefit with intensive statin therapy, compared with a relatively low risk of new-onset diabetes mellitus. Although differences among the statins have been suggested, the association of high-dose statin therapy with diabetes mellitus is considered a class effect.[60-63] For any individual who is high risk or who is at risk for diabetes, it is reasonable to monitor for glucose changes, which can include fasting glucose, HbA_{1c}, and postprandial glucose.

Blood pressure

The cardiovascular benefits associated with lowering BP are also well established. As with dyslipidemia, the BP goal is based on risk factors and risk equivalents. In most people, BP <140/90 mm Hg is appropriate.[64] The selection of antihypertensive therapy is based on concomitant diseases and patient characteristics **(FIGURE)**.

Monotherapy is often not effective in reaching the BP targets, as antihypertensive agents only provide modest BP reductions at recommended initial doses **(TABLE 2)**.[65-73] Consequently, current guidelines recommend initiating antihypertensive therapy with 2 agents for patients with stage 2 hypertension (BP ≥160/100 mm Hg).[64]

Smoking cessation

Tobacco dependence is a chronic disease that often requires repeated intervention and multiple attempts to quit. Because

FIGURE ABCD approach to initial antihypertensive therapy[16]

A	B
• ACE-I (preferred) or ARB –Diabetes mellitus –Proteinuria/chronic kidney disease –Post-MI (ACE-I) –Congestive heart failure • Aldosterone antagonist (diuretic) –Congestive heart failure –Treatment-resistant hypertension	• β-blocker –People who need rate control -Post-MI -Congestive heart failure
C	**D**
• Calcium channel blocker –People who need vasodilation -Smoker -Alcohol abuse -High salt intake	• Diuretic (thiazide or loop) –Congestive heart failure –Edema

ACE-I, angiotensin-converting enzyme inhibitor; ARB, angiotensin receptor blocker; MI, myocardial infarction

Reprinted with permission from *The Journal of Family Practice*. © 2012. Cobble ME. Coronary heart disease in men. *J Fam Pract*. 2012;61(6 suppl):S29-S33.

TABLE 2 Typical blood pressure reduction at initial doses with antihypertensive agents as monotherapy[65-73]

Antihypertensive class	Blood pressure reduction (systolic/diastolic; mm Hg)
α-adrenergic blockers	8/5
Angiotensin-converting enzyme inhibitors	8/5 – 11/6
Angiotensin receptor blockers	8/5 – 12/7
Diuretic, aldosterone antagonist	21/7
Diuretic, thiazide	6/3 – 8/4
Diuretic, loop	8/4

the health and socioeconomic consequences of tobacco use are enormous and the health benefits of smoking cessation for women are significant,[74,75] a multidisciplinary panel of the US Public Health Service concluded that it is essential that clinicians and health care delivery systems consistently identify and document tobacco use status and treat every tobacco user seen.[76] The panel further recommended that clinicians should offer every patient who uses tobacco at least the brief treatments shown to be effective. At a minimum, this includes counseling and medication, preferably in combination, as this is more effective than either alone. Effective counseling approaches include individual, group, and telephone counseling. The 2 most effective components of counseling are practical counseling (problem solving and skills training) and social support. Medications approved for smoking cessation include nicotine replacement products as well as bupropion and varenicline, which do not contain nicotine. Nicotine replacement products are available without prescription (gum, lozenge, skin patch) and by prescription (nasal spray, oral inhaler).[77] Patient education resources are available from the following websites:

Be Tobacco Free: http://betobaccofree.hhs.gov/

Smoke Free: http://www.smokefree.gov/

Centers for Disease Control and Prevention – Smoking Cessation: http://www.cdc.gov/tobacco/data_statistics/fact_sheets/cessation/quitting/index.htm

FDA 101 – Smoking Cessation Products: http://www.fda.gov/forconsumers/consumerupdates/ucm198176.htm

American Cancer Society – Guide to Quitting Smoking: http://www.cancer.org/healthy/stayawayfromtobacco/guidetoquittingsmoking/index

American Lung Association – Stop Smoking: http://www.lung.org/stop-smoking/

SUMMARY

Coronary heart disease results in a worse prognosis following a primary event in women than in men, thus demonstrating the critical importance of primary prevention in at-risk individuals beginning early in adulthood. A medical history, physical examination, laboratory determination of lipid and HbA_{1c} levels, as well as assessment of psychosocial factors, including tobacco use, provide a good initial estimate of cardiovascular risk in women. Women with coronary ischemia often present atypically, without dramatic chest pain, but with more subtle symptoms. Assessing traditional risk factors, as well as long-term risk screening, may help identify the higher-risk patients for evaluation and treatment. Statin therapy is generally used to lower LDL-C, whereas antihypertensive therapy is selected based on patient comorbidities and drug side effects. Addressing lifestyle and psychosocial factors is an important part of a comprehensive plan for cardiovascular risk reduction in women. ●

REFERENCES

1. Go AS, Mozaffarian D, Roger VL, et al; American Heart Association Statistics Committee and Stroke Statistics Committee. Heart disease and stroke statistics—2013 update: a report from the American Heart Association. *Circulation*. 2013;127(1):e6-e245.
2. Ford ES, Capewell S. Coronary heart disease mortality among young adults in the U.S. from 1980 through 2002: concealed leveling of mortality rates. *J Am Coll Cardiol*. 2007;50(22):2128-2132.

3. US Centers for Disease Control and Prevention. CDC WONDER online database, compiled from compressed mortality file 1999-2010; May 6 2013. http://wonder.cdc.gov/mortsql.html. Accessed January 2, 2014.
4. Reynolds HR, Srichai MB, Iqbal SN, et al. Mechanisms of myocardial infarction in women without angiographically obstructive coronary artery disease. *Circulation.* 2011;124(13):1414-1425.
5. Tamis-Holland JE, Lu J, Bittner V, et al; BARI 2D Study Group. Sex, clinical symptoms, and angiographic findings in patients with diabetes mellitus and coronary artery disease (from the Bypass Angioplasty Revascularization Investigation [BARI] 2 Diabetes trial). *Am J Cardiol.* 2011;107(7):980-985.
6. Gulati M, Shaw LJ, Bairey Merz CN. Myocardial ischemia in women: lessons from the NHLBI WISE study. *Clin Cardiol.* 2012;35(3):141-148.
7. Bairey Merz CN, Mark S, Boyan BD, et al. Proceedings from the scientific symposium: sex differences in cardiovascular disease and implications for therapies. *J Womens Health (Larchmt).* 2010;19(6):1059-1072.
8. Lansky A, Elashoff MR, Ng V, et al. A gender-specific blood-based gene expression score for assessing obstructive coronary artery disease in nondiabetic patients: results of the Personalized Risk Evaluation and Diagnosis in the Coronary Tree (PREDICT) trial. *Am Heart J.* 2012;164(3):320-326.
9. Lansky AJ, Ng VG, Maehara A, et al. Gender and the extent of coronary atherosclerosis, plaque composition, and clinical outcomes in acute coronary syndromes. *JACC Cardiovasc Imaging.* 2012;5(3 Suppl):S62-S72.
10. Mosca L, Hammond G, Mochari-Greenberger H, Towfighi A, Albert MA; American Heart Association Cardiovascular Disease and Stroke in Women and Special Populations Committee of the Council on Clinical Cardiology, Council on Epidemiology and Prevention, Council on Cardiovascular Nursing, Council on High Bloo. Fifteen-year trends in awareness of heart disease in women: results of a 2012 American Heart Association national survey. *Circulation.* 2013;127(11):1254-1263.
11. Flink LE, Sciacca RR, Bier ML, Rodriguez J, Giardina EG. Women at risk for cardiovascular disease lack knowledge of heart attack symptoms. *Clin Cardiol.* 2013;36(3):133-138.
12. Giardina EG, Sciacca RR, Foody JM et al. The DHHS Office on Women's Health Initiative to Improve Women's Heart Health: focus on knowledge and awareness among women with cardiometabolic risk factors. *J Womens Health (Larchmt).* 2011;20(6):893-900.
13. Yoon PW, Tong X, Schmidt SM, Matson-Koffman D. Clinical preventive services for patients at risk for cardiovascular disease, National Ambulatory Medical Care Survey, 2005-2006. *Prev Chronic Dis.* 2011;8(2):A43.
14. Schmittdiel JA, Traylor A, Uratsu CS, Mangione CM, Ferrara A, Subramanian U. The association of patient-physician gender concordance with cardiovascular disease risk factor control and treatment in diabetes. *J Womens Health (Larchmt).* 2009;18(12):2065-2070.
15. Pregler J, Freund KM, Kleinman M, et al. The heart truth professional education campaign on women and heart disease: needs assessment and evaluation results. *J Womens Health (Larchmt).* 2009;18(10):1541-1547.
16. Cobble ME. Coronary heart disease in men. *J Fam Pract.* 2012;61(6 suppl):S29-S33.
17. Bittner V, Johnson BD, Zineh I, et al. The triglyceride/high-density lipoprotein cholesterol ratio predicts all-cause mortality in women with suspected myocardial ischemia: a report from the Women's Ischemia Syndrome Evaluation (WISE). *Am Heart J.* 2009;157(3):548-555.
18. McQueen MJ, Hawken S, Wang X, et al; INTERHEART study investigators. Lipids, lipoproteins, and apolipoproteins as risk markers of myocardial infarction in 52 countries (the INTERHEART study): a case-control study. *Lancet.* 2008;372(9634):224-233.
19. Yusuf S, Hawken S, Ounpuu S, et al; INTERHEART Study Investigators. Effect of potentially modifiable risk factors associated with myocardial infarction in 52 countries (the INTERHEART study): case-control study. *Lancet.* 2004;364(9438):937-952.
20. Hokanson JE, Austin MA. Plasma triglyceride level is a risk factor for cardiovascular disease independent of high-density lipoprotein cholesterol level: a meta-analysis of population-based prospective studies. *J Cardiovasc Risk.* 1996;3(2):213-219.
21. Sarwar N, Danesh J, Eiriksdottir G, et al. Triglycerides and the risk of coronary heart disease: 10,158 incident cases among 262,525 participants in 29 Western prospective studies. *Circulation.* 2007;115(4):450-458.
22. Huxley RR, Woodward M. Cigarette smoking as a risk factor for coronary heart disease in women compared with men: a systematic review and meta-analysis of prospective cohort studies. *Lancet.* 2011;378(9799):1297-1305.
23. Mensah GA, Brown DW, Croft JB, Greenlund KJ. Major coronary risk factors and death from coronary heart disease: baseline and follow-up mortality data from the Second National Health and Nutrition Examination Survey (NHANES II). *Am J Prev Med.* 2005;29(5 Suppl 1):68-74.
24. Rallidis LS, Kotakos C, Sourides V, et al. Attainment of optional low-density lipoprotein cholesterol goal of less than 70 mg/dl and impact on prognosis of very high risk stable coronary patients: a 3-year follow-up. *Expert Opin Pharmacother.* 2011;12(10):1481-1489.
25. Davidson MH, Maki KC, Pearson TA, et al. Results of the National Cholesterol Education (NCEP) Program Evaluation ProjecT Utilizing Novel E-Technology (NEPTUNE) II survey and implications for treatment under the recent NCEP Writing Group recommendations. *Am J Cardiol.* 2005;96(4):556-563.
26. Kitkungvan D, Lynn Fillipon NM, Dani SS, Downey BC. Low-density lipoprotein cholesterol target achievement in patients at high risk for coronary heart disease. *J Clin Lipidol.* 2010;4(4):293-297.
27. Egan BM, Zhao Y, Axon RN. US trends in prevalence, awareness, treatment, and control of hypertension, 1988-2008. *JAMA.* 2010;303(20):2043-2050.
28. US Centers for Disease Control and Prevention. State-specific prevalence of cigarette smoking and smokeless tobacco use among adults—United States, 2009. *MMWR Morb Mortal Wkly Rep.* 2010;59(43):1400-1406.
29. US Centers for Disease Control and Prevention. Vital signs: prevalence, treatment, and control of hypertension--United States, 1999-2002 and 2005-2008. *MMWR Morb Mortal Wkly Rep.* 2011;60(4):103-108.
30. Berry JD, Dyer A, Cai X, et al. Lifetime risks of cardiovascular disease. *N Engl J Med.* 2012;366(4):321-329.
31. Lewis SJ, Fox KM, Grandy S; SHIELD Study Group. Self-reported diagnosis of heart disease: results from the SHIELD study. *Int J Clin Pract.* 2009;63(5):726-734.
32. Rutledge T, Linke SE, Johnson BD, et al. Self-rated versus objective health indicators as predictors of major cardiovascular events: the NHLBI-sponsored Women's Ischemia Syndrome Evaluation. *Psychosom Med.* 2010;72(6):549-555.
33. Low CA, Thurston RC, Matthews KA. Psychosocial factors in the development of heart disease in women: current research and future directions. *Psychosom Med.* 2010;72(9):842-854.
34. Wilkins R. Work stress raises risk of heart disease among women under 50, study finds. *BMJ.* 2010;340:c2508.
35. Thurston RC, Kubzansky LD. Women, loneliness, and incident coronary heart disease. *Psychosom Med.* 2009;71(8):836-842.
36. Fagring AJ, Kjellgren KI, Rosengren A, Lissner L, Manhem K, Welin C. Depression, anxiety, stress, social interaction and health-related quality of life in men and women with unexplained chest pain. *BMC Public Health.* 2008;8:165.
37. Whittaker KS, Krantz DS, Rutledge T, et al. Combining psychosocial data to improve prediction of cardiovascular disease risk factors and events: The National Heart, Lung, and Blood Institute—sponsored Women's Ischemia Syndrome Evaluation study. *Psychosom Med.* 2012;74(3):263-270.
38. Strodl E, Kenardy J. A history of heart interventions moderates the relationship between psychological variables and the presence of chest pain in older women with self-reported coronary heart disease. *Br J Health Psychol.* 2013;18(4):687-706.
39. McSweeney JC, O'Sullivan P, Cleves MA, et al. Racial differences in women's prodromal and acute symptoms of myocardial infarction. *Am J Crit Care.* 2010;19(1):63-73.
40. McSweeney JC, Cleves MA, Zhao W, Lefler LL, Yang S. Cluster analysis of women's prodromal and acute myocardial infarction symptoms by race and other characteristics. *J Cardiovasc Nurs.* 2010;25(4):311-322.
41. Brunzell JD, Davidson M, Furberg CD, et al. Lipoprotein management in patients with cardiometabolic risk: consensus conference report from the American Diabetes Association and the American College of Cardiology Foundation. *J Am Coll Cardiol.* 2008;51(15):1512-1524.
42. National Cholesterol Education Program (NCEP) Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults (Adult Treatment Panel III). Third Report of the National Cholesterol Education Program (NCEP) Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults (Adult Treatment Panel III) final report. *Circulation.* 2002;106(25):3143-3421.
43. Mosca L, Benjamin EJ, Berra K, et al; American Heart Association. Effectiveness-based guidelines for the prevention of cardiovascular disease in women--2011 update: a guideline from the American Heart Association. *Circulation.* 2011;123(11):1243-1262.
44. Hoevenaar-Blom MP, Nooyens AC, Kromhout D, et al. Mediterranean style diet and 12-year incidence of cardiovascular diseases: the EPIC-NL cohort study. *PLOS One.* 2012;7(9):e45458.
45. Fung TT, Rexrode KM, Mantzoros CS, Manson JE, Willett WC, Hu FB. Mediterranean diet and incidence of and mortality from coronary heart disease and stroke in women. *Circulation.* 2009;119(8):1093-1100.
46. Estruch R, Ros E, Salas-Salvado J, et al; PREDIMED Study Investigators. Primary prevention of cardiovascular disease with a Mediterranean diet. *N Engl J Med.* 2013;368(14):1279-1290.
47. Shepherd J, Cobbe SM, Ford I, et al. Prevention of coronary heart disease with pravastatin in men with hypercholesterolemia. West of Scotland Coronary Prevention Study Group. *N Engl J Med.* 1995;333(20):1301-1307.
48. Downs JR, Clearfield M, Weis S, et al. Primary prevention of acute coronary events with lovastatin in men and women with average cholesterol levels: results of AFCAPS/TexCAPS. Air Force/Texas Coronary Atherosclerosis Prevention Study. *JAMA.* 1998;279(20):1615-1622.
49. Sever PS, Dahlof B, Poulter NR, et al; ASCOT investigators. Prevention of coronary and stroke events with atorvastatin in hypertensive patients who have average or lower-than-average cholesterol concentrations, in the Anglo-Scandinavian Cardiac Outcomes Trial—Lipid Lowering Arm (ASCOT-LLA): a multicentre randomised controlled trial. *Lancet.* 2003;361(9364):1149-1158.
50. Ridker PM, Danielson E, Fonseca, FA et al; JUPITER Study Group. Rosuvastatin to prevent vascular events in men and women with elevated C-reactive protein. *N Engl J Med.* 2008;359(21):2195-2207.
51. Baigent C, Blackwell L, Emberson J, et al; Cholesterol Treatment Trialists' (CTT)

Collaboration. Efficacy and safety of more intensive lowering of LDL cholesterol: a meta-analysis of data from 170,000 participants in 26 randomised trials. *Lancet*. 2010;376(9753):1670-1681.
52. Delahoy PJ, Magliano DJ, Webb K, Grobler M, Liew D. The relationship between reduction in low-density lipoprotein cholesterol by statins and reduction in risk of cardiovascular outcomes: an updated meta-analysis. *Clin Ther*. 2009;31(2): 236-244.
53. Chan DK, O'Rourke F, Shen Q, Mak JC, Hung WT. Meta-analysis of the cardiovascular benefits of intensive lipid lowering with statins. *Acta Neurol Scand*. 2011;124(3): 188-195.
54. Nicholls SJ, Ballantyne CM, Barter PJ, et al. Effect of two intensive statin regimens on progression of coronary disease. *N Engl J Med*. 2011;365(22):2078-2087.
55. Baigent C, Keech A, Kearney PM, et al; Cholesterol Treatment Trialists' (CTT) Collaborators. Efficacy and safety of cholesterol-lowering treatment: prospective meta-analysis of data from 90,056 participants in 14 randomised trials of statins. *Lancet*. 2005;366(9493):1267-1278.
56. Bulbulia R, Bowman L, Wallendszus K, et al; Heart Protection Study Collaborative Group. Effects on 11-year mortality and morbidity of lowering LDL cholesterol with simvastatin for about 5 years in 20,536 high-risk individuals: a randomised controlled trial. *Lancet*. 2011;378(9808):2013-2020.
57. Sever PS, Chang CL, Gupta AK, Whitehouse A, Poulter NR; ASCOT Investigators. The Anglo-Scandinavian Cardiac Outcomes Trial: 11-year mortality follow-up of the lipid-lowering arm in the U.K. *Eur Heart J*. 2011;32(20):2525-2532.
58. Koh KK, Quon MJ, Han SH, Lee Y, Kim SJ, Shin EK. Atorvastatin causes insulin resistance and increases ambient glycemia in hypercholesterolemic patients. *J Am Coll Cardiol*. 2010;55(12):1209-1216.
59. Rajpathak SN, Kumbhani DJ, Crandall J, Barzilai N, Alderman M, Ridker PM. Statin therapy and risk of developing type 2 diabetes: a meta-analysis. *Diabetes Care*. 2009;32(10):1924-1929.
60. Preiss D, Seshasai SR, Welsh P, et al. Risk of incident diabetes with intensive-dose compared with moderate-dose statin therapy: a meta-analysis. *JAMA*. 2011;305(24):2556-2564.
61. Saku K, Zhang B, Noda K. Randomized head-to-head comparison of pitavastatin, atorvastatin, and rosuvastatin for safety and efficacy (quantity and quality of LDL): the PATROL trial. *Nihon Naika Gakkai Zasshi*. 2011;100(12):3679-3686.
62. Yokote K, Saito Y; CHIBA. Influence of statins on glucose tolerance in patients with type 2 diabetes mellitus: subanalysis of the collaborative study on hypercholesterolemia drug intervention and their benefits for atherosclerosis prevention (CHIBA study). *J Atheroscler Thromb*. 2009;16(3):297-298.
63. Preiss D, Sattar N. Statins and the risk of new-onset diabetes: a review of recent evidence. *Curr Opin Lipidol*. 2011;22(6):460-466.
64. James PA, Oparil S, Carter BL, et al. 2014 Evidence-Based Guideline for the Management of High Blood Pressure in Adults: Report From the Panel Members Appointed to the Eighth Joint National Committee (JNC 8) [published online ahead of print December 18, 2013]. *JAMA*. 2013;doi:10.1001/jama.2013.284427.
65. Heran BS, Galm BP, Wright JM. Blood pressure lowering efficacy of alpha blockers for primary hypertension. *Cochrane Database Syst Rev*. 2012;8:CD004643.
66. Heran BS, Wong MM, Heran IK, Wright JM. Blood pressure lowering efficacy of angiotensin receptor blockers for primary hypertension. *Cochrane Database Syst Rev*. 2008;4:CD003822.
67. Nixon RM, Muller E, Lowy A, Falvey H. Valsartan vs. other angiotensin II receptor blockers in the treatment of hypertension: a meta-analytical approach. *Int J Clin Pract*. 2009;63(5):766-775.
68. Zhenfeng Z, Huilan S, Junya J, Dong L, Shan L. A systematic review and meta-analysis of candesartan and losartan in the management of essential hypertension. *J Renin Angiotensin Aldosterone Syst*. 2011;12(3):365-374.
69. Kjeldsen SE, Stalhammar J, Hasvold P, Bodegard J, Olsson U, Russell D. Effects of losartan vs candesartan in reducing cardiovascular events in the primary treatment of hypertension. *J Hum Hypertens*. 2010;24(4):263-273.
70. Heran BS, Wong MM, Heran IK, Wright JM. Blood pressure lowering efficacy of angiotensin converting enzyme (ACE) inhibitors for primary hypertension. *Cochrane Database Syst Rev*. 2008;4:CD003823.
71. Batterink J, Stabler SN, Tejani AM, Fowkes CT. Spironolactone for hypertension. *Cochrane Database Syst Rev*. 2010;8:CD008169.
72. Chen JM, Heran BS, Wright JM. Blood pressure lowering efficacy of diuretics as second-line therapy for primary hypertension. *Cochrane Database Syst Rev*. 2009;4:CD007187.
73. Musini VM, Rezapour P, Wright JM, Bassett K, Jauca CD. Blood pressure lowering efficacy of loop diuretics for primary hypertension. *Cochrane Database Syst Rev*. 2012;8:CD003825.
74. Sandhu RK, Jimenez MC, Chiuve SE, et al. Smoking, smoking cessation, and risk of sudden cardiac death in women. *Circ Arrhythm Electrophysiol*. 2012;5(6): 1091-1097.
75. Pirie K, Peto R, Reeves GK, Green J, Beral V; Million Women Study Collaborators. The 21st century hazards of smoking and benefits of stopping: a prospective study of one million women in the UK. *Lancet*. 2013;381(9861):133-141.
76. US Department of Health and Human Services. Treating tobacco use and dependence: 2008 update. http://www.ahrq.gov/clinic/tobacco/treating_tobacco_use08.pdf. Published 2008. Accessed January 2, 2014.
77. US Food and Drug Administration. FDA 101: Smoking cessation products. http://www.fda.gov/downloads/ForConsumers/ConsumerUpdates/UCM331925.pdf. Published 2012. Accessed January 2, 2014.

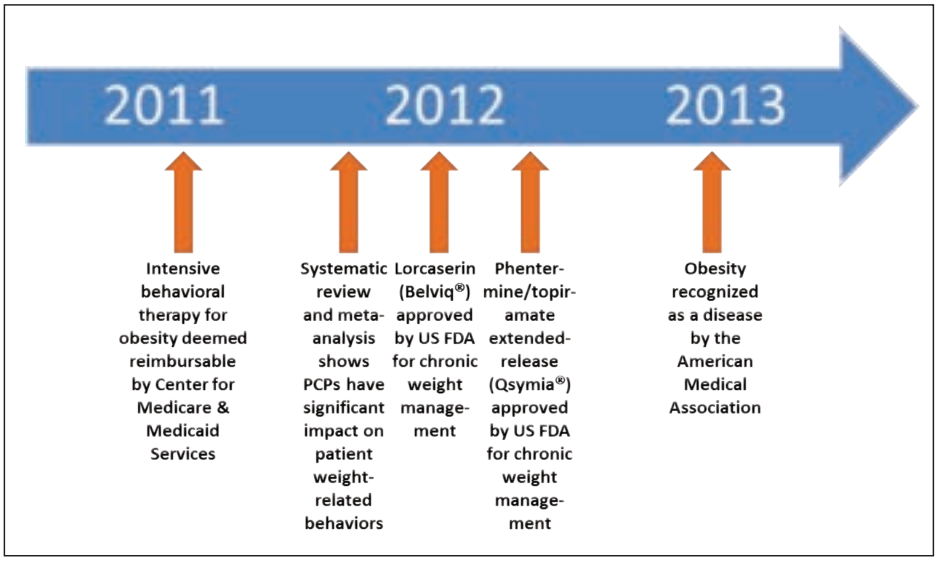
Obesity in Women

Donna H. Ryan, MD and Jill Braverman-Panza, RPh, MD

INTRODUCTION

Several developments regarding obesity management have occurred within the past 2 years that have important implications for family physicians (**FIGURE**). First, effective November 29, 2011, the Centers for Medicare and Medicaid Services approved Medicare coverage for intensive behavioral therapy for obesity as a stand-alone billable service.[1] Second, the American Medical Association adopted a policy on June 18, 2013, recognizing obesity as a disease requiring a range of medical interventions to advance obesity treatment and prevention.[2] In addition, the US Food and Drug Administration approved 2 medications, lorcaserin (Belviq) and phentermine/topiramate extended-release (Qsymia), as adjuncts to a reduced-calorie diet and increased physical activity for chronic weight management in adults with an initial body mass index (BMI) ≥30 kg/m^2 or BMI ≥27 kg/m^2 in the presence of at least 1 weight-related comorbid condition (eg, hypertension, dyslipidemia, type 2 diabetes mellitus [T2DM]).[3,4] Finally, a recent systematic review and meta-analysis involving 207,226 individuals (60% female) demonstrated the positive impact of primary care physician advice on patient engagement in weight loss efforts (odds ratio, 3.85; 95% confidence interval: 2.71-5.49; $P < .01$).[5]

FIGURE Recent events related to obesity[1-4]



Abbreviations: FDA, Food and Drug Administration; PCP, primary care physician.

These developments are important for several reasons, one of which is that health care providers contend daily with obesity and its health effects. In 1999-2000, 33.4% of women and 27.5% of men were obese (BMI ≥30 kg/m^2). In 2009-2010, the prevalence had increased in women to 35.8% and dramatically in men to 35.5%.[6] Perhaps most alarming is that the prevalence of extreme obesity (BMI >40 kg/m^2) rose from 3.9% to 6.6% of the US population (70% increase) from 2000 to 2010. The prevalence of extreme obesity is about 50% higher among women than men.[7]

Donna H. Ryan, MD, Pennington Biomedical Research Center, Baton Rouge, LA

Jill Braverman-Panza, RPh, MD, Internal and Bariatric Medicine, Braverman-Panza Medical Group, Albany, NY

DISCLOSURES

Dr. Ryan discloses that she is on the advisory boards for Eisai, Inc.; Takeda Pharmaceutical Companies Limited; and Vivus, Inc. She discloses she has ownership interest in Scientific Intake Limited Co.

Dr. Braverman-Panza discloses that she is on the advisory boards for Bristol-Myers Squibb Company and Novo Nordisk, Inc. She is on the speakers' bureaus for Boehringer-Ingelheim GmbH; Forest Pharmaceuticals, Inc.; Janssen Pharmaceuticals, Inc.; and Vivus, Inc.

SUPPORT

This article is sponsored by PCEC and is supported by funding from Novo Nordisk, Inc.

In addition to the possibility of social stigmatization and discrimination, obesity is associated with numerous health problems, including cardiovascular disease, T2DM, cancer, musculoskeletal conditions, and sleep apnea, as well as increased mortality.[8-11] In obese women, a higher risk of endometrial, cervical, breast, and possibly ovarian cancer is observed. Obesity is also associated with depression, menorrhagia, amenorrhea, stress incontinence, polycystic ovary syndrome, and infertility in women, while obesity during pregnancy is associated with negative fetal outcomes.[8,10]

Conversely, weight loss in obese individuals is associated with a lower incidence of health problems.[12-18] Modest weight loss (5%-10%) can prevent the development of T2DM in susceptible individuals as shown by a 58% reduction over 3 years in the Diabetes Prevention Program.[19] The Look AHEAD trial (N = 5145), a large, long-term study of the health benefits of lifestyle intervention for weight loss, demonstrated the benefits of modest weight loss. These included improvements in glycemic control, blood pressure (BP), blood lipids, and overall fitness that began shortly after lifestyle intervention, with a mean weight loss of 8.6% at 1 year compared with 1% weight loss in the diabetes support group.[20] Women tended to exhibit slightly slower but more sustained weight loss.[21,22] There were also reductions in the use of diabetes medications, with some patients experiencing diabetes remission; improvements in symptoms of depression, urinary stress incontinence, sexual dysfunction, and sleep apnea; and protection from loss of mobility.[12,23-27]

Approaching obesity as a chronic disease is critical and is supported by the frequent observation that weight loss is commonly observed with treatment, but weight regain typically occurs once treatment ends.[28] Furthermore, a systematic review and meta-analysis found extended care to be effective in providing sustained weight loss.[29] This article discusses multimodal approaches to obesity and its management as a chronic disease in women.

ASSESSMENT AND CLASSIFICATION

Assessment of risk posed by obesity is foundational to determining intensity of treatment. In routine clinical practice, 2 surrogate measures are utilized to assess the degree of body fat before and during treatment: BMI and waist circumference. While BMI is based on height and weight, regardless of gender, and is an accurate measure of total body fat on a population basis, BMI overestimates body fat in individuals with edema and in those who are very muscular. Conversely, BMI underestimates body fat in those who have lost muscle mass (eg, elderly) or are limited in stature.[8] Although the definition of obesity and overweight are not standardized, the US Centers for Disease Control and Prevention define obesity in adults as a BMI ≥30 kg/m^2 and overweight as a BMI between 25 and 29.9 kg/m^2.

Waist circumference is a practical surrogate measure of abdominal visceral fat.[8] Waist circumference is measured at the level of the iliac crest at the end of normal expiration, with the tape measure snug but not compressing the skin and parallel to the floor. A waist circumference >35 inches (88 cm) in women and >40 inches (102 cm) in men is considered a cardiovascular risk factor.[8] Of course, assessment of risk factors for obesity-related comorbidities is foundational, and BP, lipids, and glycemic measures all contribute to risk assessment of overweight and obese patients. The Edmonton Obesity Staging System, which includes these and other variables, can be used to stage obesity for the purposes of guiding intervention (http://www.drsharma.ca/edmonton-obesity-staging-system.html).

A brief behavioral assessment is recommended, as the findings may be helpful in determining when and what treatment should be initiated. Employing motivational interviewing (http://www.motivationalinterview.org/) and assessing "stage of change" (http://www.uri.edu/research/cprc/transtheoretical.htm) may be helpful.[30] Past weight loss attempts, treatments utilized, and reasons and barriers for success or failure should be determined, as should the presence of an eating disorder. When the patient is seeking assistance with weight loss, the reasons should be identified. In women, a desire to change body image is common.[31,32]

MANAGEMENT

Goals

There are 2 broad goals for weight management: (1) reduce the risk of obesity-related comorbidities and (2) reduce and maintain the desired body weight over the long term. To reduce body weight, a daily energy deficit of ~500-1000 kcal is generally targeted.[8] While patients often wish to lose at least 30% of body weight, a more realistic goal is 10% within 6 months.[8,32-35] It should be noted that setting realistic goals does not lead to more favorable weight loss outcomes, but not addressing patient expectations may lead to patient disappointment.[33,34,36]

General considerations

Several overarching management considerations should be kept in mind. As noted above, obesity should be managed using the chronic care model. In the same way that a patient with diabetes or hypertension is managed to achieve and maintain glycemic or BP targets, the obese patient should be managed to achieve and maintain individualized weight-related targets. As a largely self-managed disease, achieving and maintaining these targets depends on a patient's knowl-

edge, skills, and self-efficacy, with support and coaching provided by the health care team.[30,37]

Treatment of obesity requires a long-term, multimodal regimen consisting of behavior/nutrition therapy and increased physical activity, as the combination of the 2 is more effective than either alone.[38] Pharmacotherapy can be used as an adjunct to diet and exercise. Because obesity is a chronic disease, medications should be considered only as part of a long-term treatment strategy.[8] Surgery is an option for patients with BMI ≥40 kg/m^2 or BMI ≥35 kg/m^{2}and serious comorbidities.[8,39]

Continued weight loss beyond 6 months is often difficult due to changes in the metabolic rate and problems with adherence.[8] When this occurs, treatment needs to be adjusted to recreate an energy deficit to allow the patient to continue to lose weight. Once further weight loss is not achievable, treatment should focus on weight maintenance and avoidance of weight regain. In practice, patients are advised to monitor weight frequently and if regain of 5 pounds or more occurs, then the same strategies that produced successful weight loss (eg, meal replacements, food diaries, exercise intensification) should be reinstituted. If the patient wishes to lose more weight after a period of weight maintenance, further therapy aimed at weight loss can be initiated.[8]

Finally, when managing other patient conditions, medications that are associated with weight loss rather than weight gain should be used. For example, antidepressants that are associated with weight loss or are weight-neutral (bupropion, venlafaxine, or desvenlafaxine) may be better choices for treatment of depression than selective serotonin reuptake inhibitors (particularly citalopram, mirtazapine, and paroxetine) or tricyclic antidepressants, which are associated with weight gain. For T2DM, weight-neutral medications such as metformin or a dipeptidyl peptidase-4 inhibitor, or medications with a weight-lowering effect such as a glucagon-like peptide-1 receptor agonist or sodium glucose cotransporter-2 inhibitor, are appropriate.[40,41] For essential hypertension, older beta-blockers, such as atenolol, metoprolol, and propranolol, are more likely to cause weight gain than newer beta-blockers or other antihypertensives, such as angiotensin-converting enzyme inhibitors or angiotensin receptor blockers, which are weight-neutral.

Behavior therapy

Since obesity results from chronic caloric intake in excess of the body's needs, behavior modification related to nutrition and physical activity is essential. Changing behavior requires that the patient has the needed knowledge and skills for self-management and is motivated and ready to make the necessary changes. Motivational interviewing or transtheoretical model stages of change (see "Assessment and Classification," page S16) can be used to help motivate patients to change and resolve feelings of ambivalence.

A systematic review and meta-analysis of 38 trials involving 13,495 individuals showed that behavioral interventions intended to address barriers to good nutrition and exercise habits resulted in an average weight loss of 4% over 12 to 18 months.[17] A wide variety of interventions targeting behaviors to produce dietary caloric reduction and increased physical activity were employed, with some interventions delivered via telephone. Higher treatment intensity, consisting of self-monitoring, goal setting, more frequent follow-up, and making plans to address barriers to maintaining lifestyle changes over time, resulted in a 6% weight loss.[17] In general, behavioral interventions were found to lead to less weight loss in women than in men.

Self-monitoring involves the use of food diaries, physical activity logs, and weight records to enable patients to observe and record target behaviors to identify problematic patterns of behavior. Another behavior therapy approach is stimulus control, which involves patients avoiding cues that trigger unhealthy habits such as overeating and physical inactivity. Examples of stimulus control strategies include eating only at predetermined times; bringing lunch to work; placing sneakers at the door as a reminder to exercise; not buying or limiting access to unhealthy foods and beverages; and engaging in some activity immediately after eating to avoid dessert. Additional behavior therapies include cognitive restructuring (changing negative thought patterns), problem solving (preparing strategies to deal with challenging situations), and stress management.[42] As shown by the Look AHEAD trial, when other tools such as meal replacements are added to higher intensity treatment approaches, weight loss can approach 9% at 1 year.[20]

Nutrition and physical activity

Just as women are at greater risk for development of obesity and especially severe obesity, women are more likely to seek weight loss therapy. The clinical trials that evaluate nutrition and physical activity interventions regularly enroll a majority of participants who are women; it is not unusual for the participant population to be 80% female. Still, lacking evidence of gender differences in response to specific therapies, men and women generally receive the same intervention prescriptions.

Achieving weight loss requires creating an energy deficit, while sustaining a reduced weight requires embedding the habits to sustain a new lifestyle. The usual strategy is to modify behaviors that contribute to an unhealthy lifestyle and to build a series of new habits while successfully sustaining them. To avoid overwhelming the patient, not all new habits are implemented at once, but the "build" is to add subsequent habits. Successful implementation can build patient confidence and enhance motivation for more extensive changes.

Observations from the National Weight Control Registry (http://www.nwcr.ws/stories.htm) demonstrate that weight loss can be achieved with self-help methods and that while a variety of dietary paths can lead to successful weight loss, maintenance of that loss is associated with self-monitoring behaviors, good dietary habits (such as eating breakfast), and a physically active lifestyle over the long-term.[43]

Many types of diet approaches result in beneficial weight loss, regardless of the macronutrient featured or the dietary pattern, and none appear to have any long-term metabolic advantage over others in terms of weight loss.[44] What is important is the creation of an energy deficit, whether it is by counting calories or avoiding classes of foods so as to restrict food choices, with resultant reduced caloric intake. The selection of diet composition can be influenced by patient preferences and the patient's health status. It is possible to lose weight with various diets, such as the Dietary Approaches to Stop Hypertension (DASH) diet for hypertension, a vegetarian diet, a low glycemic index diet, or the Mediterranean diet.[45] Meal replacements (commercially available liquid, bar, or frozen entrees or snacks) can help in weight loss because they represent convenient sources of nutrition and have known caloric content. When used as part of a comprehensive lifestyle intervention, meal replacements can produce enhanced weight loss compared with lifestyle counseling alone. Reports involving commercial weight loss programs, such as Jenny Craig, NutriSystem, Weight Watchers, and Slimming World, suggest similar success at achieving weight losses of 5% to 10% with no greater risks than other dietary approaches.[46-51] Ultimately, the best diet is one that leads to weight loss and that the patient is able to adopt long-term to support weight maintenance.

With respect to physical activity, the amount of weight lost due to exercise is generally small due to the difficulty most patients have in maintaining a moderate- or high-intensity level of physical activity.[52] Still, the quantity of exercise can be a good predictor of success during a weight loss effort.[53] Additionally, exercise can mitigate some of the health consequences of obesity.[42] The American College of Sports Medicine recommends moderate-intensity physical activity 150 to 250 minutes/week, with an energy equivalent of 1200 to 2000 kcal/week. This level of physical activity is expected to prevent weight gain greater than 3% in most adults and may result in modest weight loss.[52]

Medications

Medications are generally recommended as adjunctive therapy in patients with BMI ≥30 kg/m^2 or BMI ≥27 kg/m^2 with other risk factors or diseases. Except orlistat, which promotes malabsorption of dietary fat, most weight loss medications promote satiety and reduce appetite. Medications can help more patients achieve clinically significant weight loss (>5%) and thus, be more likely to achieve health benefits. Medications can also be used to sustain weight loss. One principle of using weight loss medication is to use them only if they are effective. Efficacy for the medications approved for long-term use is generally based on achieving weight loss of at least 3% to 5% at 12 weeks. If this benchmark is not achieved, the dose of the medication should be increased, if appropriate, or the medication discontinued.

Currently available medications for weight loss are indicated for short- or long-term use (**TABLE**). Those used for short-term use (ie, benzphetamine, diethylpropion, phendimetrazine, phentermine) are associated with modest weight loss.[54-57] Their long-term use is not supported by clinical trials. In addition, state regulations generally limit their use to 3 months. Because of their sympathomimetic properties, they are contraindicated in many disorders, such as cardiovascular disease (eg, hypertension, advanced arteriosclerosis), hyperthyroidism, and glaucoma, during pregnancy or nursing, and in individuals with a history of drug abuse.

The efficacy and safety of the 3 medications for long-term use (ie, lorcaserin, orlistat, phentermine/topiramate) have been demonstrated in randomized trials up to 2 or 4 years.[3,4,58] In these trials, the majority of subjects were women; however, differences in outcomes between women and men were generally not provided. A review of 12 trials found that orlistat combined with behavior therapy was associated with weight loss of 5 to 10 kg (8% of baseline body weight) over 12 months compared with 3 to 6 kg (5% of baseline body weight) with placebo and the same behavior therapy.[17] Gastrointestinal adverse events were common, generally occurring early after the initiation of orlistat. Orlistat has been shown to be effective in helping maintain weight loss up to 4 years.[59]

Three clinical trials investigated lorcaserin in 6989 patients (79.0% female) over 1 year.[60-62] In these trials, lorcaserin 10 mg twice daily resulted in a weight loss of 4.5% to 5.8% compared with 1.5% to 2.8% for placebo ($P < .001$). More patients with lorcaserin lost ≥5% of their body weight compared with placebo (37.5% to 47.5% vs 16.1% to 25.0%, respectively; $P < .001$).[60-62] From a baseline of 36 kg/m^2, BMI decreased 2.1 kg/m^2 in patients treated with lorcaserin and 0.8 to 1.0 kg/m^2 in those treated with placebo; a similar reduction was seen in women and men.[60,61] Waist circumferences decreased 6.3 to 6.8 cm with lorcaserin compared with 3.9 to 4.1 cm with placebo ($P < .001$). A 4% to 6% improvement in triglycerides was observed, while improvements in other cardiovascular biomarkers were not consistently observed. Quality of life was also significantly improved.[60,61] Adverse events included upper respiratory infections, headache, dizziness, nasopharyngitis, nausea, fatigue, and back pain.

The combination of controlled-release phentermine/topiramate has been investigated in two 56-week clinical trials involving 3754 patients (74.2% women) and a 52-week

TABLE Basic pharmacology of medications indicated for weight management[3,4,54-58]

Generic	Class	Major action	Schedule
Approved for short-term use			
Benzphetamine (Didrex)	Sympathomimetic	Suppress appetite	III
Diethylpropion (Tenuate)	Sympathomimetic	Suppress appetite	IV
Phendimetrazine (Bontril)	Sympathomimetic	Suppress appetite	III
Phentermine (Adipex-P, Suprenza)	Sympathomimetic	Suppress appetite	IV
Approved for long-term use			
Lorcaserin (Belviq)	Serotonin 2C receptor agonist	Suppress appetite, promote satiety	IV
Orlistat (Xenical; Alli)	Reversible inhibitor of gastrointestinal lipases	Reduce fat absorption in gastrointestinal tract	-
Phentermine/topiramate (Qsymia)	Sympathomimetic/ gamma-aminobutyrate agonist	Suppress appetite, promote satiety	IV

extension trial.[63-65] In one 56-week trial, patients (baseline BMI, 42 kg/m^2) in the phentermine/topiramate 3.75/23 mg, phentermine/topiramate 15/92 mg, and placebo groups lost 5.1%, 10.9%, and 1.6% of their baseline body weight, respectively.[63] Weight loss ≥5% was observed in 44.9% and 66.7% of phentermine/topiramate patients, respectively, and 17.3% of placebo patients (P < .0001). Waist circumference decreased 5.6%, 10.9%, and 3.1%, respectively (P < .0001). The phentermine/topiramate 15/92 mg group had significantly greater improvement relative to placebo for systolic and diastolic BP, fasting glucose, triglycerides, total cholesterol, low-density lipoprotein cholesterol (LDL-C), and high-density lipoprotein cholesterol (HDL-C). The most common adverse events were paresthesia, dry mouth, constipation, dysgeusia, and insomnia.

In the second 56-week trial, patients (baseline BMI, 36.6 kg/m^2) in the phentermine/topiramate 7.5/46 mg and phentermine/topiramate 15/92 mg groups lost 7.8% and 9.8% of their body weight, respectively, compared with 1.2% for placebo (P < .0001).[64] Waist circumference decreased 7.6%, 9.2%, and 2.4%, respectively (P < .0001). In patients treated with phentermine/topiramate, significant improvements were observed in systolic and diastolic BP, fasting glucose, glycated hemoglobin, triglycerides, total cholesterol, LDL-C, and HDL-C. Adverse events were similar to those in the other 56-week trial, although depression- and anxiety-related adverse events were observed in a small proportion. Similar efficacy results were observed in those who continued for an additional 52 weeks (N = 676).[65] The rates of adverse events were generally reduced compared with rates in the 56-week phase.

SUMMARY

Obesity is a common disorder affecting approximately 1 in 3 women. Assessment should consist of measuring BMI and waist circumference, a thorough history regarding nutrition, physical activity, and prior attempts at weight loss, and identification of obesity-related comorbidities. As a chronic disease, obesity requires management using a chronic care model employing multimodal therapy. Behavioral therapy to bring about changes in nutrition and physical activity can be supplemented with long-term use of medications (lorcaserin, orlistat, phentermine/topiramate) to help patients both achieve and maintain meaningful weight loss. ●

REFERENCES

1. Centers for Medicare & Medicaid Services. US Department of Health and Human Services. Intensive Behavioral Therapy (IBT) for Obesity. http://www.cms.gov/Outreach-and-Education/Medicare-Learning-Network-MLN/MLNProducts/downloads/ICN907800.pdf. Published August 2012. Accessed January 2, 2014.
2. American Medical Association. AMA adopts new policies on second day of voting at annual meeting. Obesity as a disease. http://www.ama-assn.org/ama/pub/news/news/2013/2013-06-18-new-ama-policies-annual-meeting.page. Published June 18, 2013. Accessed January 2, 2014.
3. Belviq [package insert]. Woodcliff Lake, NJ: Eisai Inc.; 2012.
4. Qsymia [package insert]. Mountain View, CA: Vivus, Inc.; 2013.
5. Rose SA, Poynter PS, Anderson JW, Noar SM, Conigliaro J. Physician weight loss advice and patient weight loss behavior change: a literature review and meta-analysis of survey data. *Int J Obes (Lond).* 2013;37(1):118-128.
6. Ogden CL, Carroll MD, Kit BK, Flegal KM. Prevalence of obesity in the United States, 2009-2010. *NCHS Data Brief.* 2012;(82):1-8.
7. Sturm R, Hattori A. Morbid obesity rates continue to rise rapidly in the United States. *Int J Obes (Lond).* 2013;37(6):889-891.
8. National Institutes of Health. National Heart, Lung, and Blood Institute. North American Association for the Stuyd of Obesity. The Practical Guide: Identification, Evaluation, and Treatment of Overweight and Obesity in Adults. http://www.nhlbi.nih.gov/guidelines/obesity/prctgd_c.pdf. Published 2000. Accessed January 2, 2014.
9. Ostchega Y, Hughes JP, Terry A, Fakhouri TH, Miller I. Abdominal obesity, body mass index, and hypertension in US adults: NHANES 2007-2010. *Am J Hypertens.* 2012;25(12):1271-1278.
10. Kulie T, Slattengren A, Redmer J, Counts H, Eglash A, Schrager S. Obesity and women's health: an evidence-based review. *J Am Board Fam Med.* 2011;24(1):75-85.
11. Flegal KM, Kit BK, Orpana H, Graubard BI. Association of all-cause mortality with overweight and obesity using standard body mass index categories: a systematic review and meta-analysis. *JAMA.* 2013;309(1):71-82.
12. Rejeski WJ, Ip EH, Bertoni AG, et al; Look AHEAD Research Group. Lifestyle change and mobility in obese adults with type 2 diabetes. *N Engl J Med.* 2012;366(13):1209-1217.
13. Espeland MA, Rejeski WJ, West DS, et al; Action for Health in Diabetes Research Group. Intensive weight loss intervention in older individuals: results from the Action for Health in Diabetes Type 2 Diabetes Mellitus trial. *J Am Geriatr Soc.* 2013;61(6):912-922.
14. Williamson DA, Rejeski J, Lang W, Van Dorsten B, Fabricatore AN, Toledo K; Look AHEAD Research Group. Impact of a weight management program on health-related quality of life in overweight adults with type 2 diabetes. *Arch Intern Med.* 2009;169(2):163-171.

15. Unick JL, Beavers D, Bond DS, et al; Look AHEAD Research Group. The long-term effectiveness of a lifestyle intervention in severely obese individuals. *Am J Med.* 2013;126(3):236-242; 242.e1-242.e2.
16. Jakicic JM, Egan CM, Fabricatore AN, et al; Look AHEAD Research Group. Four-year change in cardiorespiratory fitness and influence on glycemic control in adults with type 2 diabetes in a randomized trial: the Look AHEAD Trial. *Diabetes Care.* 2013;36(5):1297-1303.
17. Leblanc ES, O'Connor E, Whitlock EP, Patnode CD, Kapka T. Effectiveness of primary care-relevant treatments for obesity in adults: a systematic evidence review for the U.S. Preventive Services Task Force. *Ann Intern Med.* 2011;155(7):434-447.
18. Ratner R, Goldberg R, Haffner S, et al; Diabetes Prevention Program Research Group. Impact of intensive lifestyle and metformin therapy on cardiovascular disease risk factors in the diabetes prevention program. *Diabetes Care.* 2005;28(4):888-894.
19. Knowler WC, Barrett-Connor E, Fowler SE, et al; Diabetes Prevention Program Research Group. Reduction in the incidence of type 2 diabetes with lifestyle intervention or metformin. *N Engl J Med.* 2002;346(6):393-403.
20. Pi-Sunyer X, Blackburn G, Brancati FL, et al; Look AHEAD Research Group. Reduction in weight and cardiovascular disease risk factors in individuals with type 2 diabetes: one-year results of the Look AHEAD trial. *Diabetes Care.* 2007;30(6):1374-1383.
21. Neiberg RH, Wing RR, Bray GA, et al; Look AHEAD Research Group. Patterns of weight change associated with long-term weight change and cardiovascular disease risk factors in the Look AHEAD Study. *Obesity (Silver Spring).* 2012;20(10):2048-2056.
22. Wadden TA, Neiberg RH, Wing RR, et al; Look AHEAD Research Group. Four-year weight losses in the Look AHEAD study: factors associated with long-term success. *Obesity (Silver Spring).* 2011;19(10):1987-1998.
23. Gregg EW, Chen H, Wagenknecht LE, et al. Association of an intensive lifestyle intervention with remission of type 2 diabetes. *JAMA.* 2012;308(23):2489-2496.
24. Faulconbridge LF, Wadden TA, Rubin RR, et al; Look AHEAD Research Group. One-year changes in symptoms of depression and weight in overweight/obese individuals with type 2 diabetes in the Look AHEAD study. *Obesity (Silver Spring).* 2012;20(4): 783-793.
25. Phelan S, Kanaya AM, Subak LL, et al; Look AHEAD Research Group. Weight loss prevents urinary incontinence in women with type 2 diabetes: results from the Look AHEAD trial. *J Urol.* 2012;187(3):939-944.
26. Foster GD, Borradaile KE, Sanders MH, et al; Sleep AHEAD Research Group of Look AHEAD Research Group. A randomized study on the effect of weight loss on obstructive sleep apnea among obese patients with type 2 diabetes: the Sleep AHEAD study. *Arch Intern Med.* 2009;169(17):1619-1626.
27. Wing RR, Bond DS, Gendrano IN III, et al; Sexual Dysfunction Subgroup of the Look AHEAD Research Group. Effect of intensive lifestyle intervention on sexual dysfunction in women with type 2 diabetes: Results from an ancillary Look AHEAD study. *Diabetes Care.* 2013;36(10):2937-2944.
28. Casazza K, Fontaine KR, Astrup A, et al. Myths, presumptions, and facts about obesity. *N Engl J Med.* 2013;368(5):446-454.
29. Middleton KM, Patidar SM, Perri MG. The impact of extended care on the long-term maintenance of weight loss: a systematic review and meta-analysis. *Obes Rev.* 2012;13(6):509-517.
30. Fitch A, Everling L, Fox C, Goldberg J, Heim C, Johnson K, Kaufman T, Kennedy E, Kestenbaun C, Lano M, Leslie D, Newell T, O'Connor P, Slusarek B, Spaniol A, Stovitz S, Webb B. Institute for Clinical Systems Improvement. Prevention and Management of Obesity for Adults. Updated May 2013. Accessed January 2, 2014.
31. Carraça EV, Silva MN, Markland D, et al. Body image change and improved eating self-regulation in a weight management intervention in women. *Int J Behav Nutr Phys Act.* 2011;8:75.
32. Siervo M, Montagnese C, Muscariello E, et al. Weight loss expectations and body dissatisfaction in young women attempting to lose weight [published online ahead of print April 19, 2013]. *J Hum Nutr Diet.* 2013;doi: 10.1111/jhn.12078.
33. Wee CC, Hamel MB, Apovian CM, et al. Expectations for weight loss and willingness to accept risk among patients seeking weight loss surgery. *JAMA Surg.* 2013;148(3):264-271.
34. White DB, Bursac Z, Dilillo V, West DS. Weight loss goals among African-American women with type 2 diabetes in a behavioral weight control program. *Obesity (Silver Spring).* 2011;19(11):2283-2285.
35. Kaly P, Orellana S, Torrella T, Takagishi C, Saff-Koche L, Murr MM. Unrealistic weight loss expectations in candidates for bariatric surgery. *Surg Obes Relat Dis.* 2008;4(1):6-10.
36. Durant NH, Joseph RP, Affuso OH, Dutton GR, Robertson HT, Allison DB. Empirical evidence does not support an association between less ambitious pre-treatment goals and better treatment outcomes: a meta-analysis. *Obes Rev.* 2013;14(7):532-540.
37. Shahnazari M, Ceresa C, Foley S, Fong A, Zidaru E, Moody S. Nutrition-focused wellness coaching promotes a reduction in body weight in overweight US veterans. *J Acad Nutr Diet.* 2013;113(7):928-935.
38. Karner-Rezek K, Knechtle B, Fenzl M, Schlegel C, Konrad M, Rosemann T. The effects of an 8-week multicomponent inpatient treatment program on body composition and anaerobic fitness in overweight and obese children and adolescents. *Int J Gen Med.* 2013;6:159-166.
39. Mechanick JI, Youdim A, Jones DB, et al; American Association of Clincial Endocrinologists; Obesity Society; American Society for Metabolic & Bariatric Surgery. Clinical practice guidelines for the perioperative nutritional, metabolic, and nonsurgical support of the bariatric surgery patient—2013 update: cosponsored by American Association of Clinical Endocrinologists, the Obesity Society, and American Society for Metabolic & Bariatric Surgery. *Endocr Pract.* 2013;19(2):337-372.
40. Inzucchi SE, Bergenstal RM, Buse JB, et al; American Diabetes Association (ADA); European Association for the Study of Diabetes (EASD). Management of hyperglycemia in type 2 diabetes: a patient-centered approach: position statement of the American Diabetes Association (ADA) and the European Association for the Study of Diabetes (EASD) [published correction appears in *Diabetes Care.* 2013;36(2):490]. *Diabetes Care.* 2012;35(6):1364-1379.
41. Garber AJ, Abrahamson MJ, Barzilay JI, et al. American Association of Clinical Endocrinologists' comprehensive diabetes management algorithm 2013 consensus statement. *Endocr Pract.* 2013;19(suppl 2):1-48.
42. McKinney L, Skolnik N, Chrusch A. American Academy of Family Physicians. Diagnosis and management of obesity. http://www.aafp.org/dam/AAFP/documents/patient_care/fitness/obesity-diagnosis-management.pdf. Published 2013. Accessed January 2, 2014.
43. Ogden LG, Stroebele N, Wyatt HR, et al. Cluster analysis of the national weight control registry to identify distinct subgroups maintaining successful weight loss. *Obesity (Silver Spring).* 2012;20(10):2039-2047.
44. Wadden TA, Webb VL, Moran CH, Bailer BA. Lifestyle modification for obesity: new developments in diet, physical activity, and behavior therapy. *Circulation.* 2012;125(9):1157-1170.
45. Ajala O, English P, Pinkney J. Systematic review and meta-analysis of different dietary approaches to the management of type 2 diabetes. *Am J Clin Nutr.* 2013;97(3):505-516.
46. Heshka S, Anderson JW, Atkinson RL, et al. Weight loss with self-help compared with a structured commercial program: a randomized trial. *JAMA.* 2003;289(14):1792-1798.
47. Rock CL, Flatt SW, Sherwood NE, Karanja N, Pakiz B, Thomson CA. Effect of a free prepared meal and incentivized weight loss program on weight loss and weight loss maintenance in obese and overweight women: a randomized controlled trial. *JAMA.* 2010;304(16):1803-1810.
48. Jebb SA, Ahern AL, Olson AD, et al. Primary care referral to a commercial provider for weight loss treatment versus standard care: a randomised controlled trial. *Lancet.* 2011;378(9801):1485-1492.
49. Jolly K, Lewis A, Beach J, et al. Comparison of range of commercial or primary care led weight reduction programmes with minimal intervention control for weight loss in obesity: lighten Up randomised controlled trial. *BMJ.* 2011;343:d6500.
50. Mitchell NS, Ellison MC, Hill JO, Tsai AG. Evaluation of the effectiveness of making Weight Watchers available to Tennessee Medicaid (TennCare) recipients. *J Gen Intern Med.* 2013;28(1):12-17.
51. Foster GD, Borradaile KE, Vander Veur SS, et al. The effects of a commercially available weight loss program among obese patients with type 2 diabetes: a randomized study. *Postgrad Med.* 2009;121(5):113-118.
52. Donnelly JE, Blair SN, Jakicic JM, Manore MM, Rankin JW, Smith BK; American College of Sports Medicine. American College of Sports Medicine Position Stand. Appropriate physical activity intervention strategies for weight loss and prevention of weight regain for adults. *Med Sci Sports Exerc.* 2009;41(2):459-471.
53. Wadden TA, West DS, Neiberg RH, et al; Look AHEAD Research Group. One-year weight losses in the Look AHEAD study: factors associated with success. *Obesity (Silver Spring).* 2009;17(4):713-722.
54. Didrex [package insert]. New York, NY: Pharmacia & Upjohn Company Division of Pfizer Inc.; August 2010.
55. Tenuate [package insert]. Bridgewater, NJ: Merrell Pharmaceuticals Inc.; November 2003.
56. Bontril [package insert]. Aliso Viejo, CA: Valeant Pharmaceuticals North America; March 2007.
57. Adipex-P [package insert]. Horsham, PA: Teva Select Brands; January 2013.
58. Xenical [package insert]. South San Francisco, CA: Genentech USA, Inc.; January 2012.
59. Torgerson JS, Hauptman J, Boldrin MN, Sjöström L. XENical in the prevention of diabetes in obese subjects (XENDOS) study: a randomized study of orlistat as an adjunct to lifestyle changes for the prevention of type 2 diabetes in obese patients [published correction appears in *Diabetes Care.* 2004;27(3):856]. *Diabetes Care.* 2004;27(1): 155-161.
60. Smith SR, Weissman NJ, Anderson CM, et al; Behavioral Modification and Lorcaserin for Overweight and Obesity Management (BLOOM) Study Group. Multicenter, placebo-controlled trial of lorcaserin for weight management. *N Engl J Med.* 2010;363(3):245-256.
61. Fidler MC, Sanchez M, Raether B, et al; BLOSSOM Clinical Trial Group. A one-year randomized trial of lorcaserin for weight loss in obese and overweight adults: the BLOSSOM trial. *J Clin Endocrinol Metab.* 2011;96(10):3067-3077.
62. O'Neil PM, Smith SR, Weissman NJ, et al. Randomized placebo-controlled clinical trial of lorcaserin for weight loss in type 2 diabetes mellitus: the BLOOM-DM study. *Obesity (Silver Spring).* 2012;20(7):1426-1436.
63. Allison DB, Gadde KM, Garvey WT, et al. Controlled-release phentermine/topiramate in severely obese adults: a randomized controlled trial (EQUIP). *Obesity (Silver Spring).* 2012;20(2):330-342.
64. Gadde KM, Allison DB, Ryan DH, et al. Effects of low-dose, controlled-release, phentermine plus topiramate combination on weight and associated comorbidities in overweight and obese adults (CONQUER): a randomised, placebo-controlled, phase 3 trial [published correction appears in *Lancet.* 2011;377(9776):1494]. *Lancet.* 2011;377(9774):1341-1352.
65. Garvey WT, Ryan DH, Look M, et al. Two-year sustained weight loss and metabolic benefits with controlled-release phentermine/topiramate in obese and overweight adults (SEQUEL): a randomized, placebo-controlled, phase 3 extension study. *Am J Clin Nutr.* 2012;95(2):297-308.

Type 2 Diabetes Mellitus in Women

Penny Tenzer-Iglesias, MD, FAAFP

Individualizing the care of patients with type 2 diabetes mellitus (T2DM) is important because of the numerous factors that affect outcomes and because T2DM is a largely self-managed disease. Among the factors to consider, patient gender is essential since there are significant differences between women and men with T2DM. One obvious difference is that women can develop gestational diabetes. Other differences between men and women with T2DM are the focus of this article, including risk factors for developing T2DM, cardiovascular and other complications, and treatment [for a focus on diabetes in men, see: Aguilar R. *J Fam Pract.* 2012;61(6):S16-S21].

KEY RISK FACTORS FOR TYPE 2 DIABETES MELLITUS IN WOMEN

Working with women to prevent the development of T2DM is an important objective for primary care clinicians. Women identified at increased risk of T2DM, especially those with prediabetes, should be educated about the disease and its risk factors, particularly modifiable risk factors such as increased body weight, lack of physical activity, elevated blood pressure (BP), elevated blood lipids, impaired glucose tolerance, and smoking. Women with nonmodifiable risk factors, such as a family history of diabetes mellitus, those who delivered a baby weighing more than 9 pounds, or those with a history of gestational diabetes, should also be educated.[1]

Women with risk factors that pose a greater risk for T2DM compared with men are especially important targets for education. One of these risk factors is the triglyceride level. A recent analysis of 2523 adults showed that the relative risk (RR) for T2DM in those with a triglyceride level in the 90% quantile (≥202 mg/dL for women vs ≥334 mg/dL for men) was higher in women than in men (4.4 vs 2.8, respectively).[2] Dyslipidemia (low high-density lipoprotein cholesterol [HDL-C], high total cholesterol, and high triglyceride level) has been shown to be significantly associated with occupational stress, particularly in women (odds ratio [OR], 1.54 vs 1.31 in men).[3] In fact, the association of occupational stress with T2DM is stronger in women than in men (OR, 2.4 in women, 1.21 in men).

The Monitoring of Trends and Determinants in Cardiovascular Disease Augsburg (MONICA) surveys involving 85 women and 128 men identified that physical inactivity (during leisure time) was an independent risk factor for T2DM in women (hazard ratio [HR], 1.80).[4] Physical inactivity was identified as spending less than 1 hour per week in a sports activity during summer or winter. Subsequent multivariate analysis of a larger cohort of the MONICA surveys (N = 527 adults with T2DM) showed that the inflammatory markers C-reactive protein (CRP) and interleukin-6 (IL-6) were significantly associated with an increased risk of T2DM in women but not in men.[5] For example, comparing tertile extremes for CRP, an HR of 7.60 was observed in women compared with 1.84 in men ($P < .001$). A prospective Finnish study also showed a significantly higher risk of T2DM with increased CRP in women compared with men ($\chi^2 = 6.42$; $P < .025$).[6] Since CRP and adiposity were more strongly associated in women than in men, adiposity-related inflammation may play a greater role in the development of insulin resistance in women.

The MONICA surveys also showed an association between high alcohol intake and increased risk of T2DM in men but not in women.[4] This is in contrast to other studies that showed that moderate alcohol consumption reduced the risk of T2DM in women.[7,8] During a median follow-up of 10.3 years, Joosten et al[7] showed that, compared with women who had consumed no alcohol during their lifetimes, HRs for T2DM were 0.75 for light (0-4.9 g/d) and former drinkers, 0.48 for moderate (5.0-14.9 g/d) drinkers, and 0.54 for heavy (≥15.0 g/d) drinkers. A U-shaped relationship between alcohol consumption and T2DM risk reduction was demonstrated by Baliunas et al[8] in a meta-analysis of 20 cohort studies. For

Penny Tenzer-Iglesias, MD, FAAFP, Associate Professor of Clinical Family Medicine, Department of Family Medicine and Community Health, University of Miami Miller School of Medicine; Chief of Service, Department of Family Medicine, University of Miami Hospital, Miami, FL

DISCLOSURES
Dr. Tenzer-Iglesias discloses that she has no real or apparent conflicts of interest to report.

SUPPORT
This article is sponsored by PCEC and is supported by funding from Novo Nordisk, Inc.

women, alcohol consumption of 24 g/day was most protective, but became harmful at about 50 g/day. The benefits of alcohol consumption in healthy women and men have been linked to lower levels of CRP, IL-6, and soluble tumor necrosis factor-alpha receptors 1 and 2.[9] Links to improved insulin sensitivity, lower basal insulin secretion, and lower fasting plasma glucagon level in healthy women have also been made.[10]

These investigations suggest that risk factors for T2DM in women, in addition to those widely recognized (eg, weight, race, family history, and fat distribution), include an elevated triglyceride level and physical inactivity, as well as occupational stress and inflammatory markers (eg, CRP and IL-6). On the other hand, moderate alcohol (5-14.9 g/d) consumption may offer a protective benefit. The clinical utility of these data remains unclear and should be cautiously applied in providing individualized patient care.

Implications for treatment

Preventing or reducing the risk of T2DM onset is an important treatment goal. Several trials have shown a 34% to 43% reduction at 7 to 20 years in the rate of conversion from impaired glucose tolerance to T2DM with lifestyle intervention.[11-13] Furthermore, augmenting lifestyle intervention with stress management strategies has been shown to contribute to greater weight loss at 3 months in women with moderate to high stress levels at baseline.[14] Although no drug is approved by the US Food and Drug Administration for prediabetes, metformin, alpha-glucosidase inhibitors, and thiazolidinediones have demonstrated an ability to decrease T2DM onset to varying degrees in both men and women.[1] Issues related to the lack of continued benefit, adverse events, and cost led the American Diabetes Association/European Association for the Study of Diabetes (ADA/EASD) consensus panel to recommend metformin as the only drug for pharmacologic intervention.[15] Appropriate candidates for metformin intervention include those with impaired glucose tolerance, impaired fasting glucose, or glycated hemoglobin (HbA_{1c}) 5.7% to 6.4%. This is particularly true if, in addition, a patient has a body mass index >35 kg/m^2, age <60 years, or prior gestational diabetes mellitus.[1] By contrast, the more recent comprehensive algorithm developed by the American Association of Clinical Endocrinologists recommends metformin, acarbose, glucagon-like peptide-1 receptor (GLP-1R) agonist, or thiazolidinedione for prediabetes.[16]

As noted in the ADA/EASD 2012 consensus recommendations, the GLP-1R agonists have demonstrated improvement in 1 or more measures of pancreatic β-cell mass and function.[15,17-20] After 52 weeks, exenatide has shown significant improvement in the first- and second-phase insulin response. At 3 years, the glucose-stimulated C-peptide response was significantly lower in the exenatide group compared with the glargine group.[17] In a 26-week trial, both exenatide and liraglutide improved β-cell function as assessed by the homeostasis model of assessment-β (HOMA-B) (2.74% vs 32.12%, respectively).[19] In a 14-week extension, those switching from exenatide to liraglutide experienced an additional 14.5% increase in HOMA-B.[20] Since pancreatic β-cell dysfunction is a key pathogenic mechanism in T2DM, this potential benefit of the GLP-1R agonists may be an important consideration in managing women, as well as men, at risk for T2DM.

RISK OF COMPLICATIONS IN WOMEN WITH TYPE 2 DIABETES MELLITUS

Once diagnosed with T2DM, treatment that targets blood glucose, BP, and lipids and includes antiplatelet therapy, smoking cessation, proper nutrition, exercise, and screening for microvascular and macrovascular disease is essential for all patients. Targeting hypertriglyceridemia and physical inactivity can be particularly helpful in women. The selection and implementation of these strategies should take into account the psychosocial and coping behaviors of women.

Risk for cardiovascular disease in type 2 diabetes mellitus

Women with T2DM compared with men with T2DM are at greater risk of a cardiovascular event. One investigation involving 4.7 years of follow-up showed that women were 8 times more likely than men to experience a composite endpoint of death, acute myocardial infarction (MI), unstable angina, coronary intervention, heart failure, cerebral ischemic stroke or transient ischemic attack, or peripheral artery disease ($P < .009$).[21] Similar findings were observed from analysis of the General Practice Research Database that included more than 42,000 women and men with T2DM.[22] The stroke rate per 1000 person-years across all ages was 13.16 (95% confidence interval [CI], 12.40-13.97) in women and 10.82 (95% CI, 10.17-11.51) in men. The rate of stroke was generally lower in women than in men with T2DM aged <75 years (except those aged 45-54 years), but higher than in men aged ≥75 years. However, in both women and men, the risk for stroke in those with diabetes compared with those without diabetes was inversely associated with age, with the greatest risk in women 35 to 54 years old with diabetes (HR compared with no diabetes: 8.18 for women, 4.66 for men). No cause for the increased risk for stroke in people with diabetes compared with those without diabetes could be identified.

The metabolic syndrome is a stronger predictor of coronary heart disease (CHD) in women than in men.[23,24] Data over 6 to 8 years from the Nurses' Health Study

(N = 30, 111 women) and Health Professionals Follow-up Study (N = 16,695 men) show that the RR of CHD in individuals with the metabolic syndrome compared with those without the metabolic syndrome was higher in women than in men (RR, 3.01 vs 1.62, respectively; $P = .03$).[23]

Furthermore, women with T2DM typically have a worse prognosis than men with T2DM after MI and a higher risk of death overall from CHD.[24] Another meta-analysis of 29 studies showed that the RR of fatal MI in women with T2DM compared with men with T2DM was 1.46.[25]

The Skaraborg Project, which involved 1116 Swedish patients with hypertension and/or T2DM, provided similar findings.[26] Over 8.1 years of follow-up, the age-adjusted HR for fatal MI was 5.0 for women with T2DM vs women without T2DM and 1.9 for men with T2DM vs men without T2DM. Analysis of data from the National Health Interview Survey showed that, despite a 40% decline in cardiovascular death and a 23% decline in all-cause mortality in patients with diabetes from 1997-1998 to 2003-2004, the differences in cardiovascular outcomes between women and men with diabetes remained unchanged.[27]

Several reasons have been identified for the worse outcomes in women with T2DM. These include a more severe form of dyslipidemia and a higher prevalence of obesity in women compared with men with T2DM.[24,28] The Italian Diabetes and Informatics Study Group found that high triglyceride levels, low HDL-C levels, and microangiopathy were important risk factors for CHD in women, whereas glycemic control and hypertension were key risk factors in men with T2DM.[29] However, analysis of the Sibutramine Cardiovascular OUTcomes (SCOUT) trial, which included 7479 overweight or obese patients with T2DM and/or cardiovascular disease, found that for each 1% increase in the HbA_{1c} level, all-cause mortality increased 22% in women and 12% in men ($P = .02$).[30] Postprandial hyperglycemia, particularly after lunch, was found to be a greater risk factor for cardiovascular events (eg, MI, angina, lower limb ischemia-related amputation, any revascularization procedure) than fasting hyperglycemia in women with T2DM.[31]

Given the ongoing difference in outcomes and compounding risk factors for women with T2DM, clinicians should consider an aggressive education and management approach toward all risk factors (ie, physical inactivity, obesity, hypertriglyceridemia, low HDL-C, hypertension, and postprandial hyperglycemia) and comorbid diseases that affect mortality, morbidity, or quality of life.

Implications for treatment

Metformin, sulfonylureas, and insulin have all demonstrated microvascular risk reduction.[16] With respect to the thiazolidinediones, pioglitazone may have a modest benefit on cardiovascular events, while rosiglitazone is associated with an increased risk of MI.

The GLP-1R agonists, alpha-glucosidase inhibitors, colesevelam, and bromocriptine have all reported beneficial effects on cardiovascular biomarkers, such as BP and/or the lipid profile. The GLP-1R agonists lower systolic but not diastolic BP 1 to 7 mm Hg.[19,20,32-34] In addition, improvements in the lipid profile are observed, particularly in the triglyceride level, where a reduction of 12 to 40 mg/dL has been reported.[18,19,32,34,35] Over a mean of 3.3 years, a cardiovascular event was observed in 2.2% of patients with impaired glucose tolerance treated with acarbose compared with 4.7% treated with placebo (HR, 0.51; $P = .03$).[36] The effects of colesevelam on the lipid profile generally show a reduction in total cholesterol, but an increase in the triglyceride level.[37] Bromocriptine has been reported to reduce cardiovascular risk (composite of first MI, stroke, coronary revascularization, or hospitalization for angina or congestive heart failure) compared with placebo (1.8% vs 3.2%, respectively).[38]

Sexual and urological issues in women with diabetes

As with men, women with T2DM develop sexual and urologic complications more frequently than people without T2DM. In addition to directly causing damage to nerves and small blood vessels, diabetes can also lead to sexual problems by contributing to psychosocial comorbidities such as anxiety or depression.[39] Sexual problems, which have been reported in 42% of women with T2DM, may include vaginal dryness, diminished or lack of desire for sexual activity, and decreased or absent sexual response. Vaginal lubricants to alleviate dyspareunia secondary to dryness and counseling regarding techniques and exercises to improve sexual functioning and response may be helpful. Diabetes also leads to urologic problems in more than half of women with diabetes, including urinary tract infections, overactive bladder, poor control of sphincter muscles, and urinary retention.[39] Since urologic problems other than urinary tract infections generally evolve over time, patients may be relatively unaware of a urologic problem or may have come to accept it. Rather than simply asking, "Do you have any problems urinating?", asking specific questions is more likely to uncover a woman's urologic problems. Examples of these types of questions include "When you have the urge to urinate, do you feel the need to urinate immediately?" "Do you ever leak urine?" "How often do you urinate during the night?" These responses may be used to guide subsequent therapy, as appropriate.

TABLE 1 Psychosocial and coping characteristics of women with type 2 diabetes mellitus[40-47]

Compared with men with T2DM, women with T2DM generally:
• Experience more diabetes-related distress and a poorer sense of well-being
• Rate their health-related quality of life higher
• Are more likely to experience symptoms of depression
• Experience a more rapid deterioration in physical function
• Exercise less
• Have higher expectations regarding the benefits of self-management
• Are more informed about T2DM, particularly pharmacologic and nonpharmacologic treatment options
• Exert more effort and employ more strategies to cope with T2DM, particularly religion, active coping, and distraction
• Have greater adaptive attitudes toward T2DM
• Are influenced less by symptoms of hypoglycemia and hyperglycemia
• Visit a physician more frequently
• Perceive more support from their health care team and are influenced more by their physician
• Believe they have little family and social support and are minimally influenced by such support

Abbreviation: T2DM, type 2 diabetes mellitus.

TABLE 2 Suggestions for women at risk for or diagnosed with type 2 diabetes mellitus[a]

For women who are at risk
• Key targets
- Triglyceride level
- Smoking cessation
• Promote healthy diet, increased activity level
For women who have been diagnosed
• Key targets
- Blood glucose, particularly postprandial glucose
- Triglyceride level
• Emphasize lifestyle management to promote weight loss and increase activity level
• Emphasize the importance of self-management
• Provide ongoing education/information regarding the progressive nature of type 2 diabetes mellitus and the need to adjust treatment over time, potentially adding both oral and injectable therapies
• Counsel on possible hormonal influences on blood glucose
• Assess for sexual and urologic complications
• Assess for psychological distress, anxiety, depression, and occupational stress; manage as appropriate
• Assess for early diabetes-related complications
• Recommend a diabetes support group

[a]These suggestions are in addition to a collaborative, patient-centered approach.

PSYCHOSOCIAL WELL-BEING, BENEFITS OF SELF-CARE, AND COPING STRATEGIES

There are important differences between women and men with T2DM regarding their attitudes and beliefs about the disease (**TABLE 1**).[40-47] Several investigators, including the MONICA surveys, found that women with T2DM are significantly less likely than men to participate in leisure time physical activity and other forms of exercise.[4,5,48] Among women who exercise, walking was the most common form of physical activity. Factors that may contribute to physical inactivity include lower socioeconomic status and depression.[48,49] In addition to the impact of occupational stress as described above, psychological distress may also play an important role as women with T2DM and type D personality (high negative affectivity and social inhibition) report a more sedentary lifestyle.[50] In patients with type 1 diabetes, fear of hypoglycemia is an important cause of physical inactivity, with fear of hypoglycemia directly associated with the number of severe hypoglycemic episodes in the previous year.[51]

Understanding these gender differences and modifying how diabetes care is provided to women vs men is particularly important for patients with T2DM, since glycemic control is largely determined by patient self-management.[52] Thus, individualizing care to provide psychological and social support as well as counseling regarding exercise and physical activity would seem to be especially important in managing women with T2DM.[40] In fact, women who had participated in diabetes self-management education (DSME) were significantly more likely than those who had not participated in DSME to participate in moderate physical activity as well as to check their blood glucose and examine their feet regularly.[53]

Implications for treatment

Improving the quality of life of a woman with T2DM should be considered an important treatment goal (**TABLE 2**). Beyond involving the woman in goal setting and decision making, providing psychological and social support and DSME are recommended as important steps to improve quality of life. Barriers to physical activity and their possible solutions, as well as the possibility of depression and occupational stress as contributing factors, should be discussed. Factors beyond physical activity that might contribute to obesity, such as poor dietary habits, should be investigated. In addition, addressing barriers and concerns with pharmacologic ther-

apy, such as weight gain and fear of hypoglycemia, can lead to significant improvements in patient quality of life.[54-57] The GLP-1R agonists and dipeptidyl peptidase-4 (DPP-4) inhibitors (alogliptin, linagliptin, saxagliptin, sitagliptin), as well as thiazolidinediones, are recommended options when the goal is to avoid hypoglycemia.[58] Similarly, the GLP-1R agonists and DPP-4 inhibitors are recommended options when the goal is to avoid weight gain.[58]

SUMMARY

Women and men with T2DM share many of the same risks and challenges in managing their disease, yet there are important differences between the genders that have been highlighted in this article. Understanding and applying the knowledge of these differences in clinical practice is essential to assist women with T2DM so as to improve their diabetes self-management, function, quality of life, and clinical outcomes. Of course, as with men, prevention of diabetes remains an important management objective. ●

REFERENCES

1. American Diabetes Association. Standards of medical care in diabetes—2012. *Diabetes Care.* 2012;35(suppl 1):S11-S63.
2. Hjellvik V, Sakshaug S, Strøm H. Body mass index, triglycerides, glucose, and blood pressure as predictors of type 2 diabetes in a middle-aged Norwegian cohort of men and women. *Clin Epidemiol.* 2012;4:213-224.
3. Djindjic N, Jovanovic J, Djindjic B, Jovanovic M, Jovanovic JJ. Associations between the occupational stress index and hypertension, type 2 diabetes mellitus, and lipid disorders in middle-aged men and women. *Ann Occup Hyg.* 2012;56(9):1051-1062.
4. Meisinger C, Thorand B, Schneider A, Stieber J, Döring A, Löwel H. Sex differences in risk factors for incident type 2 diabetes mellitus: the MONICA Augsburg cohort study. *Arch Intern Med.* 2002;162(1):82-89.
5. Thorand B, Baumert J, Kolb H, et al. Sex differences in the prediction of type 2 diabetes by inflammatory markers: results from the MONICA/KORA Augsburg case-cohort study, 1984-2002. *Diabetes Care.* 2007;30(4):854-860.
6. Hu G, Jousilahti P, Tuomilehto J, Antikainen R, Sundvall J, Salomaa V. Association of serum C-reactive protein level with sex-specific type 2 diabetes risk: a prospective Finnish study. *J Clin Endocrinol Metab.* 2009;94(6):2099-2105.
7. Joosten MM, Grobbee DE, van der A DL, Verschuren WM, Hendriks HF, Beulens JW. Combined effect of alcohol consumption and lifestyle behaviors on risk of type 2 diabetes. *Am J Clin Nutr.* 2010;91(6):1777-1783.
8. Baliunas DO, Taylor BJ, Irving H, et al. Alcohol as a risk factor for type 2 diabetes: a systematic review and meta-analysis. *Diabetes Care.* 2009;32(11):2123-2132.
9. Pai JK, Hankinson SE, Thadhani R, Rifai N, Pischon T, Rimm EB. Moderate alcohol consumption and lower levels of inflammatory markers in US men and women. *Atherosclerosis.* 2006;186(1):113-120.
10. Bonnet F, Disse E, Laville M, et al; RISC Study Group. Moderate alcohol consumption is associated with improved insulin sensitivity, reduced basal insulin secretion rate and lower fasting glucagon concentration in healthy women. *Diabetologia.* 2012;55(12):3228-3237.
11. Lindström J, Ilanne-Parikka P, Peltonen M, et al; Finnish Diabetes Prevention Study Group. Sustained reduction in the incidence of type 2 diabetes by lifestyle intervention: follow-up of the Finnish Diabetes Prevention Study. *Lancet.* 2006;368(9548):1673-1679.
12. Li G, Zhang P, Wang J, et al. The long-term effect of lifestyle interventions to prevent diabetes in the China Da Qing Diabetes Prevention Study: a 20-year follow-up study. *Lancet.* 2008;371(9626):1783-1789.
13. Knowler WC, Fowler SE, Hamman RF, et al; Diabetes Prevention Program Research Group. 10-year follow-up of diabetes incidence and weight loss in the Diabetes Prevention Program Outcomes Study. *Lancet.* 2009;374(9702):1677-1686.
14. Cox TL, Krukowski R, Love SJ, et al. Stress management-augmented behavioral weight loss intervention for African American women: a pilot, randomized controlled trial. *Health Educ Behav.* 2013;40(1):78-87.
15. Inzucchi SE, Bergenstal RM, Buse JB, et al; American Diabetes Association; European Association for the Study of Diabetes. Management of hyperglycemia in type 2 diabetes: a patient-centered approach: position statement of the American Diabetes Association (ADA) and the European Association for the Study of Diabetes (EASD). *Diabetes Care.* 2012;35(6):1364-1379.
16. Garber AJ, Abrahamson MJ, Barzilay JI, et al. American Association of Clinical Endocrinologists' comprehensive diabetes management algorithm 2013 consensus statement. *Endocr Pract.* 2013;19(suppl 2):1-48.
17. Bunck MC, Cornér A, Eliasson B, et al. Effects of exenatide on measures of ß-cell function after 3 years in metformin-treated patients with type 2 diabetes. *Diabetes Care.* 2011;34(9):2041-2047.
18. DeFronzo RA, Triplitt C, Qu Y, Lewis MS, Maggs D, Glass LC. Effects of exenatide plus rosiglitazone on beta-cell function and insulin sensitivity in subjects with type 2 diabetes on metformin. *Diabetes Care.* 2010;33(5):951-957.
19. Buse JB, Rosenstock J, Sesti G, et al; LEAD-6 Study Group. Liraglutide once a day versus exenatide twice a day for type 2 diabetes: a 26-week randomised, parallel-group, multinational, open-label trial (LEAD-6). *Lancet.* 2009;374(9683):39-47.
20. Buse JB, Sesti G, Schmidt WE, et al; Liraglutide Effect Action in Diabetes-6 Study Group. Switching to once-daily liraglutide from twice-daily exenatide further improves glycemic control in patients with type 2 diabetes using oral agents. *Diabetes Care.* 2010;33(6):1300-1303.
21. Zandbergen AA, Sijbrands EJ, Lamberts SW, Bootsma AH. Normotensive women with type 2 diabetes and microalbuminuria are at high risk for macrovascular disease. *Diabetes Care.* 2006;29(8):1851-1855.
22. Mulnier HE, Seaman HE, Raleigh VS, et al. Risk of stroke in people with type 2 diabetes in the UK: a study using the General Practice Research Database. *Diabetologia.* 2006;49(12):2859-2865.
23. Pischon T, Hu FB, Rexrode KM, Girman CJ, Manson JE, Rimm EB. Inflammation, the metabolic syndrome, and risk of coronary heart disease in women and men. *Atherosclerosis.* 2008;197(1):392-399.
24. Legato MJ, Gelzer A, Goland R, et al; Writing Group for The Partnership for Gender-Specific Medicine. Gender-specific care of the patient with diabetes: review and recommendations. *Gend Med.* 2006;3(2):131-158.
25. Huxley R, Barzi F, Woodward M. Excess risk of fatal coronary heart disease associated with diabetes in men and women: meta-analysis of 37 prospective cohort studies. *BMJ.* 2006;332(7533):73-78.
26. Larsson CA, Gullberg B, Merlo J, Rastam L, Lindblad U. Female advantage in AMI mortality is reversed in patients with type 2 diabetes in the Skaraborg Project. *Diabetes Care.* 2005;28(9):2246-2248.
27. Gregg EW, Cheng YJ, Saydah S, et al. Trends in death rates among U.S. adults with and without diabetes between 1997 and 2006: findings from the National Health Interview Survey. *Diabetes Care.* 2012;35(6):1252-1257.
28. Ferrara A, Mangione CM, Kim C, et al; Translating Research Into Action for Diabetes Study Group. Sex disparities in control and treatment of modifiable cardiovascular disease risk factors among patients with diabetes: Translating Research Into Action for Diabetes (TRIAD) Study. *Diabetes Care.* 2008;31(1):69-74.
29. Avogaro A, Giorda C, Maggini M, et al; Diabetes and Informatics Study Group; Association of Clinical Diabetologists; Instituto Superiore di Sanità. Incidence of coronary heart disease in type 2 diabetic men and women: impact of microvascular complications, treatment, and geographic location. *Diabetes Care.* 2007;30(5):1241-1247.
30. Andersson C, Van Gaal L, Caterson ID, et al. Relationship between HbA(1c) levels and risk of cardiovascular adverse outcomes and all-cause mortality in overweight and obese cardiovascular high-risk women and men with type 2 diabetes. *Diabetologia.* 2012;55(9):2348-2355.
31. Cavalot F, Petrelli A, Traversa M, et al. Postprandial blood glucose is a stronger predictor of cardiovascular events than fasting blood glucose in type 2 diabetes mellitus, particularly in women: lessons from the San Luigi Gonzaga Diabetes Study. *J Clin Endocrinol Metab.* 2006;91(3):813-819.
32. Pratley RE, Nauck M, Bailey T, et al; 1860-LIRA-DPP-4 Study Group. Liraglutide versus sitagliptin for patients with type 2 diabetes who did not have adequate glycaemic control with metformin: a 26-week, randomised, parallel-group, open-label trial. *Lancet.* 2010;375(9724):1447-1456.
33. Bergenstal RM, Wysham C, Macconell L, et al; DURATION-2 Study Group. Efficacy and safety of exenatide once weekly versus sitagliptin or pioglitazone as an adjunct to metformin for treatment of type 2 diabetes (DURATION-2): a randomised trial. *Lancet.* 2010;376(9739):431-439.
34. Moretto TJ, Milton DR, Ridge TD, et al. Efficacy and tolerability of exenatide monotherapy over 24 weeks in antidiabetic drug-naive patients with type 2 diabetes: a randomized, double-blind, placebo-controlled, parallel-group study. *Clin Ther.* 2008;30(8):1448-1460.
35. Taylor K, Gurney K, Han J, Pencek R, Walsh B, Trautmann M. Exenatide once weekly treatment maintained improvements in glycemic control and weight loss over 2 years. *BMC Endocr Disord.* 2011;11:9.
36. Chiasson JL, Josse RG, Gomis R, Hanefeld M, Karasik A, Laakso M; STOP-NIDDM Tiral Research Group. Acarbose treatment and the risk of cardiovascular disease and hypertension in patients with impaired glucose tolerance: the STOP-NIDDM trial. *JAMA.* 2003;290(4):486-494.
37. Fonseca VA, Handelsman Y, Staels B. Colesevelam lowers glucose and lipid levels in type 2 diabetes: the clinical evidence. *Diabetes Obes Metab.* 2010;12(5):384-392.

38. Gaziano JM, Cincotta AH, O'Connor CM, et al. Randomized clinical trial of quick-release bromocriptine among patients with type 2 diabetes on overall safety and cardiovascular outcomes. *Diabetes Care*. 2010;33(7):1503-1508.
39. National Institute of Diabetes and Digestive and Kidney Diseases; National Institutes of Health. Sexual and urologic problems of diabetes. http://diabetes.niddk.nih.gov/dm/pubs/sup/. Updated June 29, 2012. Accessed January 2, 2014.
40. Kacerovsky-Bielesz G, Lienhardt S, Hagenhofer M, et al. Sex-related psychological effects on metabolic control in type 2 diabetes mellitus. *Diabetologia*. 2009;52(5):781-788.
41. Rubin RR, Peyrot M, Siminerio LM. Health care and patient-reported outcomes: results of the cross-national Diabetes Attitudes, Wishes and Needs (DAWN) study. *Diabetes Care*. 2006;29(6):1249-1255.
42. McCollum M, Hansen LB, Ghushchyan V, Sullivan PW. Inconsistent health perceptions for US women and men with diabetes. *J Womens Health (Larchmt)*. 2007;16(10):1421-1428.
43. Gucciardi E, Wang SC, DeMelo M, Amaral L, Stewart DE. Characteristics of men and women with diabetes: observations during patients' initial visit to a diabetes education centre. *Can Fam Physician*. 2008;54(2):219-227.
44. Chiu CJ, Wray LA. Physical disability trajectories in older Americans with and without diabetes: the role of age, gender, race or ethnicity, and education. *Gerontologist*. 2011;51(1):51-63.
45. Nielsen AB, de Fine Olivarius N, Gannik D, Hindsberger C, Hollnagel H. Structured personal diabetes care in primary health care affects only women's HbA_{1c}. *Diabetes Care*. 2006;29(5):963-969.
46. Shalev V, Chodick G, Heymann AD, Kokia E. Gender differences in healthcare utilization and medical indicators among patients with diabetes. *Public Health*. 2005;119(1):45-49.
47. Brown SA, Harrist RB, Villagomez ET, Segura M, Barton SA, Hanis CL. Gender and treatment differences in knowledge, health beliefs, and metabolic control in Mexican Americans with type 2 diabetes. *Diabetes Educ*. 2000;26(3):425-438.
48. Barrett JE, Plotnikoff RC, Courneya KS, Raine KD. Physical activity and type 2 diabetes: exploring the role of gender and income. *Diabetes Educ*. 2007;33(1):128-143.
49. Collins-McNeil JC, Holston EC, Edwards CL, Benbow D, Ford Y. Physical activity, depressive symptoms, and social support among African-American women with type 2 diabetes. *Can J Nurs Res*. 2009;41(3):24-43.
50. Nefs G, Pouwer F, Pop V, Denollet J. Type D (distressed) personality in primary care patients with type 2 diabetes: validation and clinical correlates of the DS14 assessment. *J Psychosom Res*. 2012;72(4):251-257.
51. Brazeau AS, Rabasa-Lhoret R, Strychar I, Mircescu H. Barriers to physical activity among patients with type 1 diabetes. *Diabetes Care*. 2008;31(11):2108-2109.
52. Tuerk PW, Mueller M, Egede LE. Estimating physician effects on glycemic control in the treatment of diabetes: methods, effects sizes, and implications for treatment policy. *Diabetes Care*. 2008;31(5):869-873.
53. Gumbs JM. Relationship between diabetes self-management education and self-care behaviors among African American women with type 2 diabetes. *J Cult Divers*. 2012;19(1):18-22.
54. Davies M, Speight J. Patient-reported outcomes in trials of incretin-based therapies in patients with type 2 diabetes mellitus. *Diabetes Obes Metab*. 2012;14(10):882-892.
55. Best JH, Rubin RR, Peyrot M, et al. Weight-related quality of life, health utility, psychological well-being, and satisfaction with exenatide once weekly compared with sitagliptin or pioglitazone after 26 weeks of treatment. *Diabetes Care*. 2011;34(2):314-319.
56. Bode BW, Testa MA, Magwire M, et al; LEAD-3 Study Group. Patient-reported outcomes following treatment with the human GLP-1 analogue liraglutide or glimepiride in monotherapy: results from a randomized controlled trial in patients with type 2 diabetes. *Diabetes Obes Metab*. 2010;12(7):604-612.
57. Hermansen K, Kolotkin RL, Hammer M, Zdravkovic M, Matthews D. Patient-reported outcomes in patients with type 2 diabetes treated with liraglutide or glimepiride, both as add-on to metformin. *Prim Care Diabetes*. 2010;4(2):113-117.
58. Inzucchi SE, Bergenstal RM, Buse JB, et al. Supplementary data. *Diabetes Care*. 2012;35(6):doi:10.2337/dc12-0413.

Rheumatoid Arthritis: Early Treatment With Corticosteroids and Nonsteroidal Anti-inflammatory Drugs

Gary Ruoff, MD

INTRODUCTION

Rheumatoid arthritis (RA) is a chronic inflammatory disorder that can have a tremendous impact on patient morbidity and functioning. For example, severe morning stiffness early in the course of RA has a high impact on patients' decisions to retire from working.[1] Furthermore, joint damage begins early in the course of RA and is largely irreversible.[2] While early diagnosis and initiation of recommended therapy is important, only one-quarter to one-half of patients with RA receive appropriate therapy.[3,4] Women are more likely to be afflicted with RA and to experience more severe disease with worse disability and pain compared with men.[5,6] In addition, young women, but not young men, with RA have an increased risk of bone fractures.[7]

This article highlights the early management of patients with RA, emphasizing the criteria and need for diagnosis and pharmacologic management of early RA. An overview is also provided of 3 products recently approved by the US Food and Drug Administration (FDA), as these products are combinations or modifications of agents utilized in primary care.

CONTEMPORARY MANAGEMENT OF PATIENTS WITH EARLY RHEUMATOID ARTHRITIS

Paradigmatic changes in therapeutic approaches to patients with RA have occurred in recent years due to recognition that even early disease activity negatively impacts function and causes irreversible joint damage.[8] In addition, it is established that early initiation of disease-modifying antirheumatic drug (DMARD) therapy is associated with a greater likelihood of disease remission, improved functioning and quality of life, and reduced risk of relapse.[9-15] The beneficial effects of early initiation of DMARD therapy on pain, functioning, and disease progression have been confirmed in systematic reviews conducted over the past 15 years.[16,17]

Criteria for diagnosis

Recognition of the importance of early initiation of DMARD therapy prompted the development of a new classification system that focuses on features of RA that occur at earlier stages and are associated with persistent and/or erosive disease.[18] According to this new system, developed by the American College of Rheumatology (ACR) and the European League Against Rheumatism (EULAR), classification of a patient as having definite RA is based on the confirmed presence of inflammation of the lining in at least 1 joint (synovitis), absence of an alternate diagnosis that better explains the synovitis, and achievement of a total score ≥6 (out of 10) from the individual scores in 4 domains (see **TABLE 1**).[18] Although included in the new classification system, rheumatoid factor (RF) is a marker of autoimmunity and is not diagnostic for RA. Consequently, the anticitrullinated protein antibody (ACPA) test has become more useful in clinical practice.

When there is diagnostic doubt, conventional radiography, ultrasound, or magnetic resonance imaging can be used to improve the certainty of a diagnosis of RA above clinical criteria alone.[19] Imaging of the joints using conventional radiography has been the gold standard in RA, but its sensitivity for identifying structural damage is low and it does not allow assessment of disease activity. Recommendations for the use of imaging of joints in the clinical management of RA were recently developed; those related to the diagnosis of RA are presented in **TABLE 2**.[19]

Pharmacologic management of early rheumatoid arthritis

The goal of therapy for patients with RA is remission or, at the very least, low disease activity, so as to maximize long-term health-related quality of life through control of symp-

Gary Ruoff, MD, Clinical Professor of Family Medicine, Department of Family Practice, Michigan State University College of Medicine; Director of Clinical Research, Westside Family Medical Center, Kalamazoo, MI

DISCLOSURES

Dr. Ruoff discloses that he has no real or apparent conflicts of interest to report.

SUPPORT

This article is sponsored by PCEC and is supported by funding from Horizon Pharma, Inc.

TABLE 1 **The 2010 American College of Rheumatology/European League Against Rheumatism classification criteria for rheumatoid arthritis in newly presenting patients[18]**

Target population for testing Patients who have at least 1 joint with definite clinical synovitis, with the synovitis not better explained by another disease (eg, systemic lupus erythematosus, psoriatic arthritis, gout)	
Classification criteria (total score ≥6 needed for classification as definite RA)	**SCORE**
A. Joint involvement[a]	
1 large joint[b]	0
2-10 large joints	1
1-3 small joints (with or without involvement of large joints)[c]	2
4-10 small joints (with or without involvement of large joints)	3
>10 joints (at least 1 small joint)[d]	5
B. Serology (at least 1 test result is needed for classification)[e]	
Negative RF *and* negative ACPA	0
Low-positive RF *or* low-positive ACPA	2
High-positive RF *or* high-positive ACPA	3
C. Acute-phase reactants (at least 1 test result is needed for classification)	
Normal CRP *and* normal ESR	0
Abnormal CRP *or* abnormal ESR	1
D. Duration of symptoms[f]	
<6 weeks	0
≥6 weeks	1

Abbreviations: ACPA, anticitrullinated protein antibody; CRP, C-reactive protein; ESR, erythrocyte sedimentation rate; RF, rheumatoid factor.

[a]Swollen or tender joint (excluding distal interphalangeal joints, first carpometacarpal joints, first metatarsophalangeal joints); may be confirmed by imaging evidence of synovitis.

[b]Shoulders, elbows, hips, knees, ankles.

[c]Metacarpophalangeal joints, proximal interphalangeal joints, 2nd-5th metatarsophalangeal joints, thumb interphalangeal joints, wrists.

[d]May include temperomandibular, acromioclavicular, sternoclavicular, etc.

[e]"Negative" refers to values less than upper limit of normal (ULN); low-positive refers to values higher than ULN but ≤3 times ULN; high-positive refers to >3 times ULN. Where RF is only available as positive or negative, a positive RF should be scored as low-positive for RF.

[f]Patient self-report of the duration of signs/symptoms of synovitis of joints clinically involved at time of assessment, regardless of treatment status.

Aletaha D, Neogi T, Silman AJ, et al. *Arthritis Rheum*. 2010;62(9):2569-2581. Reproduced with permission from John Wiley & Sons, Inc. © 2010, American College of Rheumatology.

toms, prevention of structural damage, and normalization of function and social participation.[2,20] Determining the goal of therapy should be a shared decision between provider and patient based on patient considerations, such as comorbidities and preferences. To achieve the goal, therapy should be directed at abrogation of inflammation by initiating DMARD therapy—as compared to analgesic therapy—as early as possible in the disease course, ideally at the time of diagnosis.

For patients with early RA (disease duration <6 months) and low disease activity or moderate to high disease activity without poor prognostic features, synthetic DMARD monotherapy is recommended.[2] Poor prognostic features include functional limitation, extraarticular disease, positive RF or ACPA, and bony erosions by radiograph.[2] Among the synthetic DMARDs (eg, azathioprine, sulfasalazine, gold), methotrexate is used most frequently because of its efficacy, both as monotherapy and in combination with biological DMARDs, as well as its good long-term safety profile.[21] Patient response should be assessed by measuring disease activity, with treatment modified as needed, using a treat-to-target approach. This approach has been shown to provide clinical benefits compared with routine care in patients with early RA.[8,20] The treat-to-target approach for RA embraces the same principles as for diabetes mellitus, dyslipidemia, and hypertension, wherein therapy is initiated to achieve the target goal within several months and therapy is modified as needed to maintain the target goal.

TABLE 2 **Recommendations for imaging to aid in the diagnosis of rheumatoid arthritis[19]**

• The presence of inflammation seen with ultrasound or MRI can be used to predict the progression to clinical RA from undifferentiated inflammatory arthritis.
• Ultrasound and MRI are superior to clinical examination in the detection of joint inflammation; these techniques should be considered for more accurate assessment of inflammation.
• CR of the hands and feet should be used as the initial imaging technique to detect damage. However, ultrasound and/or MRI should be considered if CR does not show damage and may be used to detect damage at an earlier time point (especially in early RA).
• MRI bone edema is a strong independent predictor of subsequent radiographic progression in early RA and should be considered for use as a prognostic indicator. Joint inflammation (synovitis) detected by MRI or ultrasound as well as joint damage detected by CR, MRI, or ultrasound can also be considered for the prediction of further joint damage.
• Inflammation seen on imaging may be more predictive of a therapeutic response than clinical features of disease activity; imaging may be used to predict response to treatment.

Abbreviations: CR, conventional radiography; MRI, magnetic resonance imaging; RA, rheumatoid arthritis.

Role of corticosteroids and nonsteroidal anti-inflammatory drugs in early rheumatoid arthritis

While DMARD therapy is discussed extensively in the 2012 ACR RA guidelines, there is little mention of corticosteroids and nonsteroidal anti-inflammatory drugs (NSAIDs), except that the use of intraarticular and oral corticosteroids and NSAIDs "may be important components of RA treatment."[2] The 2010 EULAR recommendations are somewhat more descriptive, noting that adding a corticosteroid "at low to moderately high doses to synthetic DMARD monotherapy (or combinations of synthetic DMARDs) provides benefit as initial short-term management, but should be tapered as rapidly as clinically feasible."[21] Another role for low-dose corticosteroid or NSAID therapy in primary care might be to provide short-term pain relief prior to establishing a diagnosis of RA or while awaiting referral to a rheumatologist.

A concern with corticosteroid and NSAID therapy is the gastrointestinal and other adverse events associated with their use.[21,22] Three new products intended to address this concern have recently been approved by the FDA. Two combine a fixed-dose of an NSAID with either esomeprazole (naproxen/esomeprazole [Vimovo]) or famotidine (ibuprofen/famotidine [Duexis]) to prevent the occurrence of ulcers and to improve adherence over combined use of individual doses. The third product is a delayed-release prednisone (Rayos) to be taken at bedtime, with prednisone released during the early morning hours to better coincide with the circadian rhythms of endogenous cortisol and symptoms of RA, both of which peak during the early morning hours.[23] All 3 products are more expensive than generic formulations.

Naproxen/esomeprazole

The safety of the fixed-dose combination of enteric-coated naproxen 500 mg and immediate-release esomeprazole magnesium 20 mg has been evaluated for 6 to 12 months in patients with RA, osteoarthritis, or some other condition requiring daily NSAIDs.[24,25] In two 6-month studies, the cumulative incidence of endoscopically-proven gastric ulcers was 4.1% to 7.1% with naproxen/esomeprazole, compared with 23.1% to 24.3% with enteric-coated naproxen ($P < .001$).[24] Dyspepsia occurred in 16.5% to 19.5% and 23.3% to 30.1% of patients, respectively. In the 12-month study, 18.8% of patients treated with naproxen/esomeprazole experienced an upper gastrointestinal adverse event, primarily dyspepsia.[25]

Ibuprofen/famotidine

The REDUCE-1 and REDUCE-2 studies compared the safety of ibuprofen 800 mg with the fixed-dose combination of ibuprofen 800 mg and famotidine 26.6 mg 3 times daily for 24 weeks in patients with no evidence of ulcers who required daily NSAID therapy; two-thirds of the patients were women.[26,27] An endoscopically-proven gastric or duodenal ulcer was observed in 26.9% of ibuprofen patients and 14.5% of ibuprofen/famotidine patients ($P < .05$) in REDUCE-1 (N = 904) and in 20.5% and 13.0% of patients, respectively (P = NS), in REDUCE-2 (N = 627).[26] Pooled results of the studies showed that the risk of a gastric or duodenal ulcer was reduced 48% with ibuprofen/famotidine. In addition, dyspepsia occurred in 8.0% of patients treated with ibuprofen and 4.7% of patients treated with ibuprofen/famotidine, while nausea occurred in 4.7% and 5.8% of patients, respectively.

Delayed-release prednisone

The efficacy and safety of delayed-release prednisone have been evaluated in the CAPRA-1 and CAPRA-2 randomized, double-blind trials of patients with RA. In CAPRA-2, the addition of delayed-release prednisone 5 mg to DMARD therapy at dinnertime for 12 weeks resulted in significantly greater improvements in RA signs and symptoms than placebo, according to ACR criteria.[28] In CAPRA-1, patients took delayed-release prednisone between 9:30 PM and 10:30 PM

or immediate-release prednisone between 6 AM and 8 AM for 12 weeks.[23] Patients continued the same dose of prednisone taken at baseline (rounded to a full milligram; mean 6.5 vs 6.7 mg/day, respectively), as well as other DMARD and NSAID therapy. At study end, morning stiffness was reduced 44 minutes (baseline 156 minutes) in the delayed-release group compared with 23 minutes (baseline 182 minutes) in the immediate-release group (P = .072). The safety profile did not differ between the 2 groups. Patients continued on or were switched to delayed-release prednisone in a 9-month open-label extension.[29] Over the 12 months of treatment, the mean morning stiffness decreased 83 minutes in the delayed-release group and 88 minutes in the immediate-release/delayed-release group. Treatment-related adverse events observed in >1.0% of the total study population were weight increase (2.4%), gastritis (1.6%), and upper abdominal pain (1.2%). Additional investigation has shown significant improvement in health-related quality of life and reduced need for biological DMARD therapy over 9 months in patients with long-standing RA.[30] The cost-effectiveness of delayed-release prednisone has yet to be compared with immediate-release prednisone.

SUMMARY

The family physician plays several important roles in the management of patients with RA by early diagnosis of RA, with initiation of synthetic DMARD therapy, and in long-term follow-up to minimize complications of DMARD therapy and its impact on patient comorbidities. Three recently approved products offer some benefit as adjunctive therapy. ●

REFERENCES

1. Westhoff G, Buttgereit F, Gromnica-Ihle E, Zink A. Morning stiffness and its influence on early retirement in patients with recent onset rheumatoid arthritis. *Rheumatology (Oxford).* 2008;47(7):980-984.
2. Singh JA, Furst DE, Bharat A, et al. 2012 update of the 2008 American College of Rheumatology recommendations for the use of disease-modifying antirheumatic drugs and biologic agents in the treatment of rheumatoid arthritis. *Arthritis Care Res (Hoboken).* 2012;64(5):625-639.
3. Solomon DH, Ayanian JZ, Yelin E, Shaykevich T, Brookhart MA, Katz JN. Use of disease-modifying medications for rheumatoid arthritis by race and ethnicity in the National Ambulatory Medical Care Survey. *Arthritis Care Res (Hoboken).* 2012;64(2):184-189.
4. Harrold LR, Harrington JT, Curtis JR, et al. Prescribing practices in a US cohort of rheumatoid arthritis patients before and after publication of the American College of Rheumatology treatment recommendations. *Arthritis Rheum.* 2012;64(3):630-638.
5. Jawaheer D, Messing S, Reed G, et al. Significance of sex in achieving sustained remission in the consortium of rheumatology researchers of North America cohort of rheumatoid arthritis patients. *Arthritis Care Res (Hoboken).* 2012;64(12):1811-1818.
6. Sokka T, Toloza S, Cutolo M, et al; QUEST-RA Group. Women, men, and rheumatoid arthritis: analyses of disease activity, disease characteristics, and treatments in the QUEST-RA study. *Arthritis Res Ther.* 2009;11(1):R7.
7. Amin S, Gabriel SE, Achenbach SJ, Atkinson EJ, Melton LJ III. Are young women and men with rheumatoid arthritis at risk for fragility fractures? A population-based study. *J Rheumatol.* 2013;40(10):1669-1676.
8. Schoels M, Knevel R, Aletaha D, et al. Evidence for treating rheumatoid arthritis to target: results of a systematic literature search [published correction appears in *Ann Rheum Dis.* 2011;70(8):1519]. *Ann Rheum Dis.* 2010;69(4):638-643.
9. Salaffi F, Carotti M, Sartini A, Cervini C. A prospective study of the long-term efficacy and toxicity of low-dose methotrexate in rheumatoid arthritis. *Clin Exp Rheumatol.* 1995;13(1):23-28.
10. Crilly A, McInness IB, McDonald AG, Watson J, Capell HA, Madhok R. Interleukin 6 (IL-6) and soluble IL-2 receptor levels in patients with rheumatoid arthritis treated with low dose oral methotrexate. *J Rheumatol.* 1995;22(2):224-226.
11. St Clair EW, van der Heijde DM, Smolen JS, et al; Active-Controlled Study of Patients Receiving Infliximab for the Treatment of Rheumatoid Arthritis of Early Onset Study Group. Combination of infliximab and methotrexate therapy for early rheumatoid arthritis: a randomized, controlled trial. *Arthritis Rheum.* 2004;50(11):3432-3443.
12. Bejarano V, Quinn M, Conaghan PG, et al; Yorkshire Early Arthritis Register Consortium. Effect of the early use of the anti-tumor necrosis factor adalimumab on the prevention of job loss in patients with early rheumatoid arthritis. *Arthritis Rheum.* 2008;59(10):1467-1474.
13. Emery P, Breedveld FC, Hall S, et al. Comparison of methotrexate monotherapy with a combination of methotrexate and etanercept in active, early, moderate to severe rheumatoid arthritis (COMET): a randomised, double-blind, parallel treatment trial. *Lancet.* 2008;372(9636):375-382.
14. Han C, Smolen J, Kavanaugh A, St Clair EW, Baker D, Bala M. Comparison of employability outcomes among patients with early or long-standing rheumatoid arthritis. *Arthritis Rheum.* 2008;59(4):510-514.
15. van der Kooij SM, le Cessie S, Goekoop-Ruiterman YP, et al. Clinical and radiological efficacy of initial vs delayed treatment with infliximab plus methotrexate in patients with early rheumatoid arthritis. *Ann Rheum Dis.* 2009;68(7):1153-1158.
16. Suarez-Almazor ME, Belseck E, Shea B, Wells G, Tugwell P. Methotrexate for rheumatoid arthritis. *Cochrane Database Syst Rev.* 2000;2:CD000957.
17. Katchamart W, Trudeau J, Phumethum V, Bombardier C. Methotrexate monotherapy versus methotrexate combination therapy with non-biologic disease modifying anti-rheumatic drugs for rheumatoid arthritis. *Cochrane Database Syst Rev.* 2010;4:CD008495.
18. Aletaha D, Neogi T, Silman AJ, et al. 2010 Rheumatoid arthritis classification criteria: an American College of Rheumatology/European League Against Rheumatism collaborative initiative. *Arthritis Rheum.* 2010;62(9):2569-2581.
19. Colebatch AN, Edwards CJ, Østergaard M, et al. EULAR recommendations for the use of imaging of the joints in the clinical management of rheumatoid arthritis. *Ann Rheum Dis.* 2013;72(6):804-814.
20. Smolen JS, Aletaha D, Bijlsma JW, et al; T2T Expert Committee. Treating rheumatoid arthritis to target: recommendations of an international task force [published corrections appear in *Ann Rheum Dis.* 2011;70(7):1349; *Ann Rheum Dis.* 2011;70(8):1519]. *Ann Rheum Dis.* 2010;69(4):631-637.
21. Smolen JS, Landewé R, Breedveld FC, et al. EULAR recommendations for the management of rheumatoid arthritis with synthetic and biological disease-modifying antirheumatic drugs [published correction appears in *Ann Rheum Dis.* 2011;70(8):1519]. *Ann Rheum Dis.* 2010;69(6):964-975.
22. van der Goes MC, Jacobs JW, Boers M, et al. Monitoring adverse events of low-dose glucocorticoid therapy: EULAR recommendations for clinical trials and daily practice. *Ann Rheum Dis.* 2010;69(11):1913-1919.
23. Buttgereit F, Doering G, Schaeffler A, et al. Efficacy of modified-release versus standard prednisone to reduce duration of morning stiffness of the joints in rheumatoid arthritis (CAPRA-1): a double-blind, randomised controlled trial. *Lancet.* 2008;371(9608):205-214.
24. Goldstein JL, Hochberg MC, Fort JG, Zhang Y, Hwang C, Sostek M. Clinical trial: the incidence of NSAID-associated endoscopic gastric ulcers in patients treated with PN 400 (naproxen plus esomeprazole magnesium) vs. enteric-coated naproxen alone. *Aliment Pharmacol Ther.* 2010;32(3):401-413.
25. Sostek MB, Fort JG, Estborn L, Vikman K. Long-term safety of naproxen and esomeprazole magnesium fixed-dose combination: phase III study in patients at risk for NSAID-associated gastric ulcers. *Curr Med Res Opin.* 2011;27(4):847-854.
26. Laine L, Kivitz AJ, Bello AE, Grahn AY, Schiff MH, Taha AS. Double-blind randomized trials of single-tablet ibuprofen/high-dose famotidine vs. ibuprofen alone for reduction of gastric and duodenal ulcers. *Am J Gastroenterol.* 2012;107(3):379-386.
27. Bello AE. DUEXIS(®) (ibuprofen 800 mg, famotidine 26.6 mg): a new approach to gastroprotection for patients with chronic pain and inflammation who require treatment with a nonsteroidal anti-inflammatory drug. *Ther Adv Musculoskelet Dis.* 2012;4(5):327-339.
28. Buttgereit F, Mehta D, Kirwan J, et al. Low-dose prednisone chronotherapy for rheumatoid arthritis: a randomised clinical trial (CAPRA-2). *Ann Rheum Dis.* 2013;72(2):204-210.
29. Buttgereit F, Doering G, Schaeffler A, et al. Targeting pathophysiological rhythms: prednisone chronotherapy shows sustained efficacy in rheumatoid arthritis. *Ann Rheum Dis.* 2010;69(7):1275-1280.
30. Pfeiffer BM, Krenzer S, Dockhorn R, et al. Impact of modified-release prednisone on functional ability in patients with rheumatoid arthritis. *Rheumatol Int.* 2012;33(6):1447-1454.

The Pharmacologic Management of Nausea and Vomiting of Pregnancy

Jennifer R. Niebyl, MD and Gerald G. Briggs, BPharm, FCCP

INTRODUCTION

Nausea and vomiting of pregnancy (NVP) is widely recognized as a common complication and occurs in 44% to 89% of pregnant women.[1] NVP usually begins between 4 and 6 weeks of gestation, peaks between 8 and 12 weeks, and resolves by 16 to 20 weeks in the majority of women.[1] Continuation beyond 20 weeks is generally thought to occur in 5% to 10% of women. However, recent evidence suggests that 29% to 45% of women experience NVP during late pregnancy, suggesting that inquiry about NVP should be made throughout a woman's pregnancy.[1,2]

Despite the high prevalence, undertreatment of NVP has been common in the United States, likely due to the beliefs that NVP is a natural part of pregnancy and that there is no need for concern unless there are signs or symptoms related to NVP in its most severe form, ie, hyperemesis gravidarum.[3] Hyperemesis gravidarum is typically characterized by persistent nausea and vomiting with or without retching, >5% weight loss, hypokalemia, high urine specific gravity due to dehydration, and ketonuria.[4] Other factors contributing to the undertreatment of NVP include fear of fetal harm caused by medications and, until recently, the lack of available prescription medications in the United States proven effective for NVP.[3]

Addressing these beliefs is important, since women who experience even mild or moderate NVP can suffer from depression and diminished functioning related to employment, household activities, parenting, and other physical and social activities. NVP can also lead to increased costs and utilization of health care resources.[5-10] While concerns about harm to the fetus due to medications are justified, many medications commonly used to treat NVP are not known to pose additional fetal risk.[11] Furthermore, initiating treatment at the recognition of pregnancy, before the occurrence of symptoms of NVP in women at high risk for recurrence of severe NVP, is superior to initiating treatment following the onset of symptoms.[12] Addressing these issues in the primary care management of the pregnant woman with nausea and vomiting is the focus of this article.

ASSESSMENT

Common symptoms associated with NVP include any combination of nausea, gagging, retching, dry heaving, vomiting, and odor and/or food aversion.[4] Since a focus of the assessment is to determine if the nausea and vomiting are due to the pregnancy or some other cause, the patient should be questioned about the onset, timing, severity, aggravating and alleviating factors, and appearance of the vomitus, as this can help to rule out causes other than pregnancy. Onset of nausea beyond 8 weeks after the last menstrual period is rare in pregnancy.[13]

NVP is often triggered by 1 or more factors, such as motion, heartburn, and food or other odors. The vomitus in NVP is usually nonbilious and nonbloody.[14] The patient history should include questions concerning fever, abdominal pain, and change in bowel habits; headache, neck stiffness, and changes in vision may suggest a neurological cause.[14]

Non–pregnancy-related causes of persistent vomiting include gastrointestinal disorders (eg, appendicitis, hepatitis, pancreatitis, biliary tract disease), pyelonephritis, metabolic disorders such as diabetic ketoacidosis, porphyria, or Addison disease, and central nervous system diseases such as migraine, infections, tumors, and seizures.[13,14] When a cause other than pregnancy is suspected, laboratory testing should

Jennifer R. Niebyl, MD, Professor and Vice-Chair, Department of Obstetrics and Gynecology, University of Iowa Hospitals and Clinics, Iowa City, IA

Gerald G. Briggs, BPharm, FCCP, Clinical Professor of Pharmacy, University of California, San Francisco, San Francisco, CA; Adjunct Professor of Pharmacy Practice, University of Southern California, Los Angeles, CA; Adjunct Professor, Department of Pharmacotherapy, Washington State University, Spokane, WA; Pharmacist Clinical Specialist (Obstetrics), Outpatient Clinics, Memorial Care Center for Women, Miller Children's Hospital, Long Beach Memorial Medical Center, Long Beach, CA

DISCLOSURES

Dr. Niebyl discloses that she has no real or apparent conflicts of interest to report.

Dr. Briggs discloses that he is on the advisory board for Duchesnay USA.

SUPPORT

This article is sponsored by PCEC and is supported by funding from Duchesnay USA.

generally assess urinary ketones, blood urea nitrogen, creatinine, alanine aminotransferase, aspartate aminotransferase, electrolytes, amylase, and thyrotropin.[13] Complications of NVP should be investigated as well, particularly in women who experience severe, persistent vomiting. Possible complications include dehydration or thiamine deficiency resulting in Wernicke encephalopathy, which can occur after 3 weeks of persistent vomiting.

The Pregnancy-Unique Quantification of Emesis (PUQE) score can be used to assess the severity of NVP, as well as to follow the response to treatment and improvement over time.[4] Both 12- and 24-hour scoring systems have been validated; the 24-hour system accounts for time sleeping and the severity of symptoms through the first trimester.[15]

Finally, the assessment should also include inquiry about treatments that have already been attempted by the patient to self-manage NVP. These include not only lifestyle and dietary changes, but also vitamins and complementary or alternative therapies.

TREATMENT

Variation in the symptoms of NVP and the impact they have on pregnant women and their families requires that treatment be individualized to achieve the following goals: 1) reduce the incidence, severity, and impact of symptoms; 2) reduce the risk of progression to more severe NVP; 3) correct the consequences or complications, including fluid/electrolyte imbalance and metabolic alkalosis; and 4) minimize the effects on the fetus, particularly the effects of treatment. To achieve these goals, nonpharmacologic therapies, followed by pharmacologic therapies if necessary, can be employed.

Nonpharmacologic and alternative therapies

A mainstay of treatment for NVP involves dietary and lifestyle approaches. Women should be advised to avoid factors that trigger nausea, including strong odors, fatty or spicy foods, and iron tablets.[13] Clinical experience indicates that avoiding an empty stomach by eating small meals consisting of bland, dry, high-protein food every 1 to 2 hours and drinking room-temperature fluids between meals (rather than with meals) may be helpful.[13,16,17] Dietary guidelines developed by the Motherisk NVP group at Toronto's Hospital for Sick Children are summarized in **TABLE 1**.[15] Beyond dietary factors, adequate sleep is also important.

Pyridoxine (vitamin B_6) and ginger are often used by patients prior to seeking medical care and have been shown to be safe and effective for NVP.[11] Pyridoxine is typically used in daily doses of 50 to 100 mg, although daily doses as high as 500 mg have been used.[18-21] Ginger is also effective in daily doses of 500 to 1000 mg, with reflux and heartburn the most common side effects.[13,22-25] A comparison of pyridoxine and ginger found ginger 1000 mg/day to be more effective than pyridoxine 40 mg/day for 4 days for reducing the severity of nausea. Both were similarly effective for decreasing the number of vomiting episodes in early pregnancy.[26]

Weak evidence indicates that acupressure may be effective for NVP.[27] Acupressure involves stimulation of the pericardium 6 (P6) acupoint, located 4.5 cm above the wrist on the inside of the forearm.[16,28-31] Stimulation is provided by wrist bands, with some emitting a weak electrical current. PrimaBella, formerly the ReliefBand, has been shown to be effective and is the only device approved by the US Food and Drug Administration (FDA) for NVP.[32,33]

TABLE 1 Dietary guidelines for nausea and vomiting of pregnancy[15]

• Maintain adequate hydration and electrolyte levels, drinking at least 2 liters of water a day
• Avoid an empty stomach at all times, with small frequent meals every 1-2 hours, consisting of bland foods throughout the day
• Prevent a full stomach (ie, not mixing solids with liquid, avoid large meals and very fatty food)
• Avoid strong-tasting, odorous foods (ie, spicy, metallic tastes)
• Snack on nuts and high-protein foods between meals
• Discontinue iron-containing prenatal multivitamins in early pregnancy and switch to children's chewable tablets and folic acid instead. Resume iron-containing prenatal vitamins after 12 weeks when iron is most needed by mother and baby. Pregnant women with past or current anemia should not discontinue prenatal vitamins, but may take them in divided doses
• Consume ice chips, ice pops, and very cold beverages to help reduce metallic taste
• Eat simple dry carbohydrates (ie, crackers, biscuits, etc) prior to getting out of bed in the morning

Pharmacologic treatment

A wide variety of pharmacologic options have been utilized for the management of NVP **(TABLE 2)**.[11,34-39] Efficacy and safety are 2 key considerations in selecting treatment. A recent systematic, evidence-based review examined randomized controlled trials of any intervention for NVP.[27] Excluded were trials using a crossover design or those involving women with hyperemesis gravidarum. Twenty-seven trials of nonpharmacologic and pharmacologic treatment involving 4041 women were included. Due to the lack of high-quality evidence, the Cochrane investigators found limited evidence to support the use of pharmacologic antiemetic agents in early pregnancy. In contrast, the American

TABLE 2 Fetal safety of pharmacologic agents used to treat nausea and vomiting of pregnancy

Pharmacologic class/agent	Risk classification	
	FDA risk factor[a]	Briggs et al[11b]
Doxylamine succinate/pyridoxine hydrochloride	A[34]	Compatible
H_1-receptor blocker		
Dimenhydrinate	Not rated	Compatible
Diphenhydramine	Not rated	Compatible
Doxylamine	Not rated	Compatible
Hydroxyzine	Not rated	Human data suggest low risk
Meclizine	Not rated	Compatible
Metoclopramide	B[35]	Compatible
Phenothiazine		
Prochlorperazine	Not rated	Compatible
Promethazine	C[36]	Compatible
Ondansetron	B[37]	Human data suggest low risk
Pyridoxine hydrochloride	A[38]	Compatible
Corticosteroid	C[39]	Human data suggest risk; avoid during first 10 weeks of gestation
Prednisone		

Abbreviation: FDA, US Food and Drug Administration.

[a]FDA risk factor definitions:

A: adequate and well-controlled human studies have failed to demonstrate a risk to the fetus in the first trimester of pregnancy (and there is no evidence of risk in later trimesters)

B: Animal reproduction studies have failed to demonstrate a risk to the fetus and there are no adequate and well-controlled studies in pregnant women OR animal studies have shown an adverse effect, but adequate and well-controlled studies in pregnant women have failed to demonstrate a risk to the fetus in any trimester

C: Animal reproduction studies have shown an adverse effect on the fetus and there are no adequate and well-controlled studies in humans, but potential benefits may warrant use of the drug in pregnant women despite potential risks.

[b]Definitions from *Drugs in Pregnancy and Lactation, 9th ed*. by Briggs, Freeman, and Yaffe:

Compatible: Human pregnancy experience is adequate to demonstrate that the embryo-fetal risk is very low or nonexistent.

Human data suggest low risk: The limited human pregnancy experience suggests that the drug does not represent a significant risk of developmental toxicity (growth restriction, structural anomalies, functional/neurobehavioral deficits, or death) at any time in pregnancy.

Human data suggest risk: The human data suggest there may be a risk for developmental toxicity throughout pregnancy. Usually, pregnancy exposure should be avoided, but the risk may be acceptable if the maternal condition requires the drug.

Congress of Obstetricians and Gynecologists (ACOG) concluded that pyridoxine alone or in combination with doxylamine is safe and effective for NVP and should be considered first-line pharmacotherapy.[40]

In considering the safety of these agents, 2 points need to be kept in mind. First, there is the inherent problem of ethically conducting trials in pregnant women to assess medication safety in humans. Thus, safety is often inferred from animal studies. For older medications, such as antihistamines and some phenothiazines, there is no FDA pregnancy rating (**TABLE 2**).[34-39] Second, the risk of having a baby with a birth defect by chance alone is 1% to 3%.[41] Meta-analyses and epidemiologic studies have not found a higher incidence of birth defects with antihistamines (H_1-receptor blockers), phenothiazines, and metoclopramide.[42-46] A marginally increased risk of major malformations following first-trimester exposure to corticosteroids has been observed.[47] In addition, the same study found an increased risk (odds ratio, 3.35) of oral cleft. An increased risk of hypospadias (odds ratio, 2.87) with corticosteroid use during the first trimester has also been identified from an analysis of data from the National Birth Defects Prevention Study.[48] These findings indicate that corticosteroids should be reserved for NVP refractory to other treatments until after the first trimester of pregnancy.

Doxylamine/pyridoxine

Bendectin, the combination of doxylamine and pyridoxine (also in combination with dicyclomine until 1978), was used as an antiemetic by more than 33 million pregnant women in the United States and throughout the world for nearly

3 decades. In the late 1970s, published studies began to appear that raised the possibility of an association of doxylamine/pyridoxine with birth defects. In-depth review by the FDA and regulatory agencies throughout the world found no association between doxylamine/pyridoxine and birth defects. Nonetheless, allegations continued and litigation mounted, causing the principal manufacturer to remove doxylamine/pyridoxine worldwide in 1983.[49] A generic form of doxylamine/pyridoxine, Diclectin, remained on the market in Canada, where it continues to be first-line therapy for NVP.[50]

Following the withdrawal of Bendectin, 2 meta-analyses involving data from more than 200,000 pregnancies found no increased risk for major malformations with exposure to doxylamine/pyridoxine.[51,52] Subsequent studies have provided further support regarding the safety of doxylamine/pyridoxine, finding no association with birth defects.[16,53] Doxylamine/pyridoxine has remained classified as risk level A in the standard reference *Drugs in Pregnancy and Lactation* by Briggs, Freeman, and Yaffe.[11] This rating was based on the authors' independent ongoing review of the evidence that found doxylamine/pyridoxine safe in human pregnancy, including in the first trimester. In 2004 and again in 2009, ACOG concluded that "treatment of nausea and vomiting of pregnancy with pyridoxine or pyridoxine plus doxylamine is safe and effective and should be considered first-line pharmacotherapy."[40]

In 2005, the manufacturer of doxylamine/pyridoxine in Canada submitted a new drug application to the FDA. As part of its review, the FDA required a new phase III placebo-controlled study to be conducted in the United States.[54] The study involved 241 women 7 to 14 weeks pregnant experiencing NVP. Results showed doxylamine/pyridoxine to be superior to placebo in improving NVP symptoms (change from baseline in the PUQE score: –4.8 vs –3.9, respectively; $P = .006$). Nineteen percent of women took 2 tablets daily, 21% took 3 tablets daily, and 60% took 4 tablets daily. Quality of life after 2 weeks was also improved and women treated with doxylamine/pyridoxine required less rescue therapy and reported fewer days missed from work. In April 2013, the FDA approved Diclegis, the combination of doxylamine succinate 10 mg plus pyridoxine hydrochloride 10 mg delayed-release tablets, for the treatment of NVP in women who do not respond to conservative management.[34] The FDA also classified the product as pregnancy category A, which is the strongest evidence of fetal safety possible.

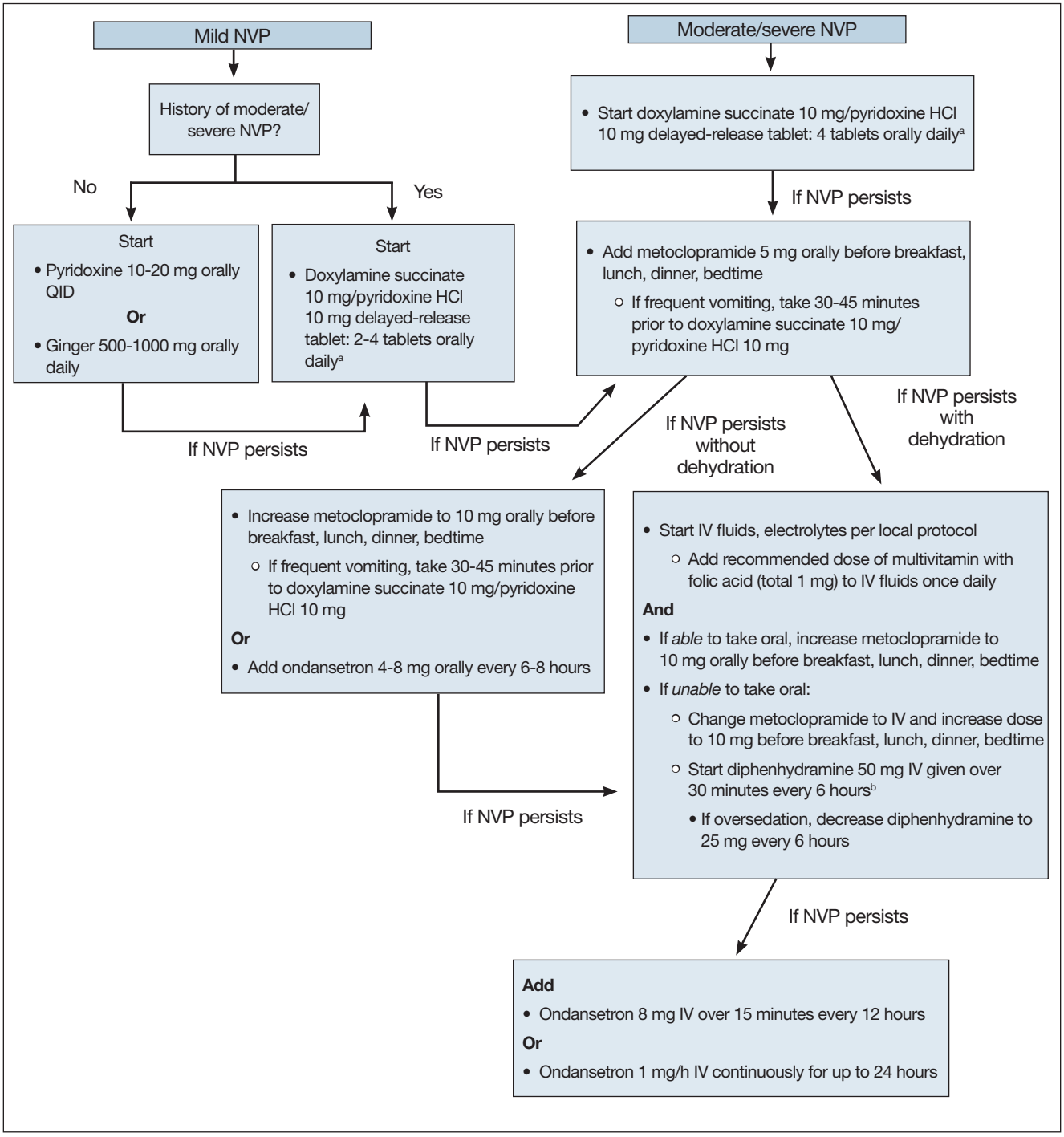
Beyond safety, clinical studies as well as clinical experience over more than 4 decades demonstrate the combination of doxylamine and pyridoxine to be effective in reducing the incidence and severity of NVP.[54] The product now available in the United States is recommended to be given as 2 tablets at bedtime. If symptoms are not adequately controlled within 24 to 48 hours, the dose can be increased to 4 tablets daily (1 tablet in the morning, 1 midafternoon, and 2 at bedtime).[34] The morning dose can be added after 1 day and the afternoon dose after another day. Somnolence is the most common adverse event observed (14.3% vs 11.7% for placebo), likely due to the anticholinergic effects of doxylamine, an H_1-receptor antagonist.[34]

Although the Cochrane systematic review cited above found only limited evidence to support the use of pharmacological antiemetic agents for NVP, clinical experience indicates that some treatment options are effective. The **FIGURE** shows a suggested approach for the pharmacologic treatment of women with NVP during early pregnancy. As the only medication approved by the FDA for NVP and as recommended by ACOG, doxylamine succinate/pyridoxine hydrochloride delayed-release tablets are first-line pharmacologic therapy.[40] For those who have an inadequate response to doxylamine succinate/pyridoxine hydrochloride delayed-release tablets, a drug from a different pharmacologic class, such as metoclopramide, should be added. This has the benefits of utilizing drugs with different mechanisms of action while reducing the likelihood of additive adverse events such as sedation. The same options are also appropriate as monotherapy for women who are intolerant of doxylamine succinate/pyridoxine hydrochloride delayed-release tablets.

Adverse events are also a consideration when selecting treatment. The use of an antihistamine (H_1-receptor antagonist) or a phenothiazine may be limited by sedation, particularly with increasing doses. Although tardive dyskinesia may occur with a phenothiazine or metoclopramide, the risk is low with the doses and duration of therapy used for NVP. Another potential complication with metoclopramide is serotonin syndrome, a potentially life-threatening set of symptoms caused by serotonin toxicity. The risk of serotonin syndrome is increased when a patient taking metoclopramide is also taking another medication that promotes serotonin activity, such as an antidepressant (selective serotonin reuptake inhibitor, serotonin and norepinephrine reuptake inhibitor, tricyclic monoamine oxidase inhibitor, or bupropion), a triptan, lithium, or ondansetron. [Note: many of these medications are categorized as pregnancy class C or D by the FDA.] Serotonin syndrome may also be possible with ondansetron and is under investigation by the FDA.[55] Ondansetron is also associated with the potential for QT prolongation; investigation to identify patients at high risk is ongoing.[56]

The fetal safety of ondansetron, a 5-hydroxytryptamine$_3$-receptor antagonist, has been investigated in a retrospective review of data from the National Birth Defects Prevention Study involving women with NVP. Compared with controls

FIGURE **Pharmacologic treatment of nausea and vomiting of pregnancy**[34,35,37,40]



Abbreviations: HCl, hydrochloride; IV, intravenous; NVP, nausea and vomiting of pregnancy; QID, 4 times daily.

[a]If 2 tablets/day, take 2 at bedtime; if 3 tablets/day, take 1 in the morning, afternoon, and bedtime; if 4 tablets/day, take 1 in the morning and afternoon and 2 at bedtime.

[b]Doxylamine and diphenhydramine are ethanolamines, a subclass of the H_1 antihistamine group. They have marked sedative properties, as well as anticholinergic and antiemetic actions. The anticholinergic action will prevent metoclopramide-related tardive dyskinesia.

Notes

Phenothiazines also cause tardive dyskinesia and would potentiate that adverse reaction if used with metoclopramide.

If NVP persists after the above therapy, hyperemesis gravidarum should be considered and, if suspected, the patient should be hospitalized.

without birth defects, children born of mothers treated with ondansetron during the first trimester showed an increased risk of cleft palate (odds ratio, 2.37).[48] The risks of nonsyndromic cleft lip with or without cleft palate, neural tube defects, and hypospadias were similar between controls and those treated with ondansetron. Recently, the results of 2 Danish studies investigating the fetal safety of ondansetron have been reported, but with opposite findings. Both were retrospective analyses based on birth defect and prescription medication information from similar registries and from overlapping time periods. One study involving 897,018 women found a doubling in the prevalence of major congenital heart defects in children whose mothers were treated with ondansetron during the first trimester of pregnancy.[57] In the other study, involving 608,385 pregnancies, there was no increased risk of stillbirth, no major birth defect, and no infants born at low birth weight or at small size for gestational age associated with ondansetron exposure.[58] However, the risk of preterm delivery was significantly increased with ondansetron (odds ratio, 1.28; 95% confidence interval, 1.05-1.55). The reason for these discrepant findings is unclear. In women with hyperemesis gravidarum refractory to standard treatment (N = 16), no teratogenic effects were observed; however, 1 minor birth defect, 2 premature births, and 6 pregnancy or neonatal adverse outcomes were observed.[59]

Referral

Pregnant women with severe symptoms of NVP, particularly those with an inadequate response to combination therapy and those who experience significant morbidity or complications, should be considered for referral to an obstetrician or treatment in the hospital.

SUMMARY

Nausea and vomiting are common in early pregnancy. Forty percent or more of pregnant women may continue to suffer beyond the first trimester and 10% beyond the second trimester. A focus of the assessment is to confirm that the nausea and vomiting is due to the pregnancy and not some other cause. Nonpharmacologic options, particularly dietary modification, are a mainstay of treatment. For those who continue to experience symptoms, pharmacologic management can be employed. The combination of doxylamine succinate/pyridoxine hydrochloride was reintroduced in the United States following FDA approval in early 2013. The product was given a pregnancy safety rating of A and is recommended as first-line pharmacologic treatment for NVP. Other options include antihistamines, metoclopramide, ondansetron, phenothiazines, and after the first trimester, corticosteroids. ●

REFERENCES

1. Einarson TR, Piwko C, Koren G. Prevalence of nausea and vomiting of pregancy in the USA: a meta analysis. *J Popul Ther Clin Pharmacol.* 2013;20(2):e163-e170.
2. Kramer J, Bowen A, Stewart N, Muhajarine N. Nausea and vomiting of pregnancy: prevalence, severity and relation to psychosocial health. *MCN Am J Matern Child Nurs.* 2013;38(1):21-27.
3. Madjunkova S, Maltepe C, Koren G. The leading concerns of American women with nausea and vomiting of pregnancy calling Motherisk NVP Helpline. *Obstet Gynecol Int.* 2013;2013:752980.
4. Clark SM, Costantine MM, Hankins GD. Review of NVP and HG and early pharmacotherapeutic intervention. *Obstet Gynecol Int.* 2012;2012:252676.
5. Smith C, Crowther C, Beilby J, Dandeaux J. The impact of nausea and vomiting on women: a burden of early pregnancy. *Aust N Z J Obstet Gynaecol.* 2000;40(4):397-401.
6. Mazzotta P, Stewart D, Atanackovic G, Koren G, Magee LA. Psychosocial morbidity among women with nausea and vomiting of pregnancy: prevalence and association with anti-emetic therapy. *J Psychosom Obstet Gynaecol.* 2000;21(3):129-136.
7. Attard CL, Kohli MA, Coleman S, et al. The burden of illness of severe nausea and vomiting of pregnancy in the United States. *Am J Obstet Gynecol.* 2002;186(5 suppl understanding):S220-S227.
8. Setse R, Grogan R, Pham L, et al. Longitudinal study of depressive symptoms and health-related quality of life during pregnancy and after delivery: the Health Status in Pregnancy (HIP) study. *Matern Child Health J.* 2009;13(5):577-587.
9. Munch S, Korst LM, Hernandez GD, Romero R, Goodwin TM. Health-related quality of life in women with nausea and vomiting of pregnancy: the importance of psychosocial context. *J Perinatol.* 2011;31(1):10-20.
10. Piwko C, Koren G, Babashov V, Vicente C, Einarson TR. Economic burden of nausea and vomiting of pregnancy in the USA. *J Popul Ther Clin Pharmacol.* 2013;20(2):e149-e160.
11. Briggs GG, Freeman RK, Yaffe SJ. *Drugs in Pregnancy and Lactation*. 9th ed. Philadelphia, PA: Lippincott Williams & Wilkins; 2011.
12. Maltepe C, Koren G. Preemptive treatment of nausea and vomiting of pregnancy: results of a randomized controlled trial. *Obstet Gynecol Int.* 2013;2013:809787.
13. Niebyl JR. Clinical practice. Nausea and vomiting in pregnancy. *N Engl J Med.* 2010;363(16):1544-1550.
14. Firoz T, Maltepe C, Einarson A. Nausea and vomiting in pregnancy is not always nausea and vomiting of pregnancy. *J Obstet Gynaecol Can.* 2010;32(10):970-972.
15. Ebrahimi N, Maltepe C, Bournissen FG, Koren G. Nausea and vomiting of pregnancy: using the 24-hour Pregnancy-Unique Quantification of Emesis (PUQE-24) scale. *J Obstet Gynaecol Can.* 2009;31(9):803-807.
16. Ebrahimi N, Maltepe C, Einarson A. Optimal management of nausea and vomiting of pregnancy. *Int J Womens Health.* 2010;2:241-248.
17. Maltepe C, Koren G. The management of nausea and vomiting of pregnancy and hyperemesis gravidarum—a 2013 update. *J Popul Ther Clin Pharmacol.* 2013;20(2):e184-e192.
18. Tan PC, Yow CM, Omar SZ. A placebo-controlled trial of oral pyridoxine in hyperemesis gravidarum. *Gynecol Obstet Invest.* 2009;67(3):151-157.
19. Shrim A, Boskovic R, Maltepe C, Navios Y, Garcia-Bournissen F, Koren G. Pregnancy outcome following use of large doses of vitamin B6 in the first trimester. *J Obstet Gynaecol.* 2006;26(8):749-751.
20. Vutyavanich T, Wongtra-ngan S, Ruangsri R. Pyridoxine for nausea and vomiting of pregnancy: a randomized, double-blind, placebo-controlled trial. *Am J Obstet Gynecol.* 1995;173(3 pt 1):881-884.
21. Sahakian V, Rouse D, Sipes S, Rose N, Niebyl J. Vitamin B6 is effective therapy for nausea and vomiting of pregnancy: a randomized, double-blind placebo-controlled study. *Obstet Gynecol.* 1991;78(1):33-36.
22. Borrelli F, Capasso R, Aviello G, Pittler MH, Izzo AA. Effectiveness and safety of ginger in the treatment of pregnancy-induced nausea and vomiting. *Obstet Gynecol.* 2005;105(4):849-856.
23. Portnoi G, Chng LA, Karimi-Tabesh L, Koren G, Tan MP, Einarson A. Prospective comparative study of the safety and effectiveness of ginger for the treatment of nausea and vomiting in pregnancy. *Am J Obstet Gynecol.* 2003;189(5):1374-1377.
24. Vutyavanich T, Kraisarin T, Ruangsri R. Ginger for nausea and vomiting in pregnancy: randomized, double-masked, placebo-controlled trial. *Obstet Gynecol.* 2001;97(4):577-582.
25. Ozgoli G, Goli M, Simbar M. Effects of ginger capsules on pregnancy, nausea, and vomiting. *J Altern Complement Med.* 2009;15(3):243-246.
26. Ensiyeh J, Sakineh MA. Comparing ginger and vitamin B6 for the treatment of nausea and vomiting in pregnancy: a randomised controlled trial. *Midwifery.* 2009;25(6):649-653.
27. Matthews A, Dowswell T, Haas DM, Doyle M, O'Mathúna DP. Interventions for nausea and vomiting in early pregnancy. *Cochrane Database Syst Rev.* 2010;(9):CD007575.
28. Lee EJ, Frazier SK. The efficacy of acupressure for symptom management: a systematic review. *J Pain Symptom Manage.* 2011;42(4):589-603.
29. Can Gürkan O, Arslan H. Effect of acupressure on nausea and vomiting during pregnancy. *Complement Ther Clin Pract.* 2008;14(1):46-52.

30. Heazell A, Thorneycroft J, Walton V, Etherington I. Acupressure for the in-patient treatment of nausea and vomiting in early pregnancy: a randomized control trial. *Am J Obstet Gynecol*. 2006;194(3):815-820.
31. Rosen T, de Veciana M, Miller HS, Stewart L, Rebarber A, Slotnick RN. A randomized controlled trial of nerve stimulation for relief of nausea and vomiting in pregnancy. *Obstet Gynecol*. 2003;102(1):129-135.
32. Slotnick RN. Safe, successful nausea suppression in early pregnancy with P-6 acustimulation. *J Reprod Med*. 2001;46(9):811-814.
33. PrimaBella. Neurowave Medical Technologies. http://www.primabellarx.com/pdf/PrimaBella-Instructions-For-Use.pdf. Published 2011. Accessed January 2, 2014.
34. Diclegis [package insert]. Bryn Mawr, PA: Duchesnay USA, Inc.; 2013.
35. Reglan [package insert]. Baudette, MN: ANI Pharmaceuticals, Inc.; 2012.
36. Phenergan [package insert]. Eatontown, NJ: West-Ward Pharmaceuticals; 2012.
37. Zofran [package insert]. Research Triangle Park, NC: GlaxoSmithKline; 2013.
38. Pyridoxine HCl [package insert]. Schaumburg, IL: APP Pharmaceuticals, LLC; 2008.
39. Prednisone [package insert]. Columbus, OH: Roxane Laboratories, Inc.; 2012.
40. American College of Obstetricians and Gynecologists. Guideline summary: nausea and vomiting of pregnancy. http://www.guideline.gov/content.aspx?id=10939&search=nausea+AND+pregnancy. Published 2009. Accessed January 2, 2014.
41. Nguyen P, Einarson A. Managing nausea and vomiting of pregnancy with pharmacological and nonpharmacological treatments. *Womens Health (Lond Engl)*. 2006;2(5):753-760.
42. Seto A, Einarson T, Koren G. Pregnancy outcome following first trimester exposure to antihistamines: meta-analysis. *Am J Perinatol*. 1997;14(3):119-124.
43. Gilboa SM, Strickland MJ, Olshan AF, Werler MM, Correa A; National Birth Defects Prevention Study. Use of antihistamine medications during early pregnancy and isolated major malformations. *Birth Defects Res A Clin Mol Teratol*. 2009;85(2):137-150.
44. Magee LA, Mazzotta P, Koren G. Evidence-based view of safety and effectiveness of pharmacologic therapy for nausea and vomiting of pregnancy (NVP). *Am J Obstet Gynecol*. 2002;186(5 suppl understanding):S256-S261.
45. Matok I, Gorodischer R, Koren G, Sheiner E, Wiznitzer A, Levy A. The safety of metoclopramide use in the first trimester of pregnancy. *N Engl J Med*. 2009;360(24):2528-2535.
46. Sørensen HT, Nielsen GL, Christensen K, Tage-Jensen U, Ekbom A, Baron J; The Euromap Study Group. Birth outcome following maternal use of metoclopramide. *Br J Clin Pharmacol*. 2000;49(3):264-268.
47. Park-Wyllie L, Mazzotta P, Pastuszak A, et al. Birth defects after maternal exposure to corticosteroids: prospective cohort study and meta-analysis of epidemiological studies. *Teratology*. 2000;62(6):385-392.
48. Anderka M, Mitchell AA, Louik C, Werler MM, Hernández-Diaz S, Rasmussen SA; National Birth Defects Prevention Study. Medications used to treat nausea and vomiting of pregnancy and the risk of selected birth defects. *Birth Defects Res A Clin Mol Teratol*. 2012;94(1):22-30.
49. Duchesnay Inc. Bendectin history. http://www.bendectin.com/en/. Published 2013. Accessed January 2, 2014.
50. Koren G. The return to the USA of doxylamine-pyridoxine delayed release combination (Diclegis®) for morning sickness—a new morning for American women. *J Popul Ther Clin Pharmacol*. 2013;20(2):e161-e162.
51. Einarson TR, Leeder JS, Koren G. A method for meta-analysis of epidemiological studies. *Drug Intell Clin Pharm*. 1988;22(10):813-824.
52. McKeigue PM, Lamm SH, Linn S, Kutcher JS. Bendectin and birth defects: I. A meta-analysis of the epidemiologic studies. *Teratology*. 1994;50(1):27-37.
53. Nulman I, Rovet J, Barrera M, Knittel-Keren D, Feldman BM, Koren G. Long-term neurodevelopment of children exposed to maternal nausea and vomiting of pregnancy and diclectin. *J Pediatr*. 2009;155(1):45-50, 50.e1-50.e2.
54. Koren G, Clark S, Hankins GD, et al. Effectiveness of delayed-release doxylamine and pyridoxine for nausea and vomiting of pregnancy: a randomized placebo controlled trial. *Am J Obstet Gynecol*. 2010;203(6):571.e1-577.e1.
55. US Food and Drug Administration. Potential signals of serious risks/new safety information identified by the FDA Adverse Event Reporting System (FAERS) between January-March 2013. http://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/Surveillance/AdverseDrugEffects/ucm351864.htm. Updated October 31, 2013. Accessed January 2, 2014.
56. US Food and Drug Administration. FDA Drug Safety Communication: Abnormal heart rhythms may be associated with use of Zofran (ondansetron). http://www.fda.gov/drugs/drugsafety/ucm271913.htm. Published September 15, 2011. Accessed January 2, 2014.
57. Andersen JT, Jimenez-Solem E, Andersen NL, Poulsen HE. Ondansetron use in early pregnancy and the risk of congenital malformations—a register based nationwide cohort study. Paper presented at: 29th International Conference on Pharmacoepidemiology & Therapeutic Risk Management; August 25-28, 2013; Montréal, Quebec, Canada.
58. Pasternak B, Svanstrom H, Hviid A. Ondansetron in pregnancy and risk of adverse fetal outcomes. *N Engl J Med*. 2013;368:814-823.
59. Ferreira E, Gillet M, Lelièvre J, Bussières JF. Ondansetron use during pregnancy: a case series. *J Popul Ther Clin Pharmacol*. 2012;19(1):e1-e10.

The Pharmacologic Management of Idiopathic Overactive Bladder in Primary Care

Pamela I. Ellsworth, MD

CONTINUING MEDICAL EDUCATION

LEARNING OBJECTIVES

After reading this article on overactive bladder, the family physician will be able to:

1. Characterize the impact of overactive bladder in women
2. Describe the role of patient education, behavioral modification, and pharmacologic treatment
3. Select antimuscarinic therapy based on patient characteristics and comorbidities
4. Describe the efficacy and safety of mirabegron and onabotulinumtoxinA

TARGET AUDIENCE

Family physicians and clinicians who wish to gain increased knowledge and greater competency regarding primary care management of idiopathic overactive bladder.

DISLCOSURES

As a continuing medical education provider accredited by the Accreditation Council for Continuing Medical Education (ACCME), it is the policy of Primary Care Education Consortium (PCEC) to require any individual in a position to influence educational content to disclose the existence of any financial interest or other personal relationship with the manufacturer(s) of any commercial product(s).

Pamela I. Ellsworth, MD discloses that she is on the advisory boards for Allergan, Inc.; Astellas Pharma US, Inc.; and Pfizer Inc. She is on the speakers' bureau for Pfizer Inc.

Allan J. Wilke MD, CME reviewer, discloses that he has no real or apparent conflicts of interest to report.

Angela Cimmino, PharmD, and Gregory Scott, PharmD, RPh, medical writers, disclose that they have no real or apparent conflicts of interest to report.

CONFLICTS OF INTEREST

When individuals in a position to control content have reported financial relationships with one or more commercial interests, Primary Care Education Consortium works with them to resolve such conflicts to ensure that the content presented is free of commercial bias. The content of this activity was vetted by the following mechanisms and modified as required to meet this standard:

- Content peer review by an external topic expert
- Content peer review by an external CME reviewer
- Content validation by internal Primary Care Education Consortium clinical editorial staff

OFF-LABEL DISCLOSURES

In accordance with ACCME guidelines, the faculty author has been asked to disclose discussion of unlabeled or unapproved uses of drugs or devices during the course of the activity.

SPONSORSHIP

This activity is sponsored by Primary Care Education Consortium and Primary Care Metabolic Group.

ACCREDITATION

This activity has been planned and implemented in accordance with the Essential Areas and policies of the Accreditation Council for Continuing Medical Education (ACCME) and Primary Care Education Consortium. Primary Care Education Consortium is accredited by the ACCME to provide continuing medical education to physicians.

AMA PRA CATEGORY 1

Primary Care Education Consortium designates this activity, "The Pharmacologic Management of Idiopathic Overactive Bladder in Primary Care," for a maximum of 1.0 AMA PRA Category 1 Credit™. Physicians should claim only the credit commensurate with the extent of their participation in the activity.

Release Date: February 1, 2014
Expiration Date: January 31, 2015

METHOD OF PARTICIPATION

PHYSICIANS
To receive CME credit, please read the journal article and on completion, go to www.pceconsortium.org/oab to complete the online post-test and receive your certificate of completion.

PHYSICIAN ASSISTANTS
AAPA accepts certificates of participation of educational activities certified for AMA PRA Category 1 Credit ™ from organizations accredited by ACCME or a recognized state medical society.

SUPPORTER

This activity was supported by an educational grant from Allergan, Inc.

CASE STUDY #1: Sally, a 53-year-old patient, mentions the following during a routine follow-up visit to her primary care physician: "I am excited but worried about my son's upcoming wedding. What happens if I have the urge to go during the ceremony and can't make it to the bathroom? That would be so embarrassing. I don't want to have to wear a diaper. I've had this problem for years, but now I am so worried. Is there anything that can be done that will work quickly since the wedding is in 4 months?"

EPIDEMIOLOGY IN WOMEN

The case study above illustrates several important issues related to overactive bladder (OAB): the significant impact on quality of life (QOL), the emotional toll, and the paradoxical delay in years for patients to seek treatment.

Urgency urinary incontinence is 1 of the symptoms commonly experienced by persons with idiopathic (ie, non-neurogenic) OAB. Overactive bladder is a symptom complex characterized by urgency (the sudden, compelling desire to void that is difficult to defer), with or without urgency urinary incontinence, often associated with frequency (8 or more micturitions during a 24-hour period), and nocturia. The etiology of OAB is multifactorial and thought to be due to detrusor overactivity and altered bladder afferent nerve activity.[1] Risk factors for OAB include advancing age, obesity, and diabetes.[2-5] Approximately 17% of adults worldwide suffer from OAB, including approximately 33 million adults in the United States.[2,6,7]

There is little difference in the prevalence of OAB in women (16.9%) and men (16.0%) in the United States, although 1 study estimated a higher prevalence in women than in men (26.1% vs 10.7%, respectively).[2,6,8] Women are more likely to experience urgency urinary incontinence (also referred to as "wet" OAB). Wet OAB increases in prevalence with age; women aged 65 years or older are 2.5 times as likely and women aged 45 to 54 years are twice as likely as women aged 18 to 34 years to experience OAB symptoms.[8] Urgency urinary incontinence is the symptom that typically prompts patients, particularly women, to seek medical care.[7,9,10]

Pamela I. Ellsworth, MD, Professor of Urology, University of Massachusetts Medical School/UMass Memorial Medical Center, Worcester, MA

DISCLOSURES

Dr. Ellsworth discloses that she is on the advisory boards for Allergan, Inc.; Astellas Pharma US, Inc.; and Pfizer Inc. She is on the speakers' bureau for Pfizer Inc.

SUPPORT

This activity is sponsored by PCEC and is supported by an educational grant from Allergan, Inc.

IMPACT AND BARRIERS TO TREATMENT

The impact of OAB on QOL is considerable, resulting in limitations on physical activities, social interactions, and travel; work absence; avoidance of sexual intimacy; guilt; and loss of self-esteem.[11-13] The negative health impacts of OAB extend "beyond the bladder" and are often underappreciated. The most prevalent comorbidities occurring in higher percentages of patients with OAB vs controls are urinary tract infections (28.0% vs 8.4%, respectively), falls and fractures (25.3% vs 16.1%), depression (10.5% vs 4.9%), and skin infections (3.9% vs 2.3%).[14] In a survey of over 6000 community-dwelling women, frequent urge incontinence was an independent risk factor for falling (odds ratio, 1.26) among women aged >65 years.[15] Incontinence is also a major factor leading to nursing home admission.[16]

Despite the considerable negative effects of OAB, it remains underdiagnosed and undertreated. Only about one-fourth to one-half of patients who have OAB ever seek medical care, and among those who do, over half remain undiagnosed.[2,9,17-19] Moreover, an analysis of over 7.2 million patients aged ≥45 years in the IMS Health data set revealed that only 24.4% of patients diagnosed with OAB were treated.[10]

Among patients who do seek medical care for OAB symptoms, more than half wait longer than a year to seek treatment and typically do so only when symptoms and/or the impact on QOL have become intolerable or, as in the case above, threaten social embarrassment.[7,9,17,20] Patient-related barriers to seeking medical care include discomfort and embarrassment with discussing the issue with a health care provider; misperceptions of a lack of available treatment options or that treatment requires surgery or invasive procedures; and misperception that OAB is a normal part of aging.[2,21] Physicians often do not ask patients about OAB symptoms due to a reliance on patient complaint to trigger action; time constraints; lack of appreciation for the impact on QOL and other potential complications; or lack of awareness of available effective treatments.[7,22]

Screening for OAB and the evaluation of OAB is relatively easily performed in the primary care setting. A history, focused physical examination (abdominal, pelvic, neurologic), and urinalysis are often all that are needed.[7,23] Further discussion of the diagnostic workup for OAB is beyond the scope of this article, but can be found in guidelines published by the American Urological Association (AUA) in 2012 (http://www.auanet.org/common/pdf/education/clinical-guidance/Overactive-Bladder.pdf).[23]

OVERVIEW OF TREATMENT

The goals of OAB treatment are to maximize symptom control and improvement in QOL while minimizing other neg-

ative health effects, treatment-related adverse events, and patient burden.[23] Factors that may affect treatment selection include the patient's ability to perceive an improvement in his or her symptoms and QOL, comorbidities, and concomitant medications.[22,23] For example, treatment-related may be inappropriate, unsafe, or futile in patients who cannot perceive symptom improvement (eg, very elderly, severely cognitively compromised).[23] However, in patients for whom hygiene and skin breakdown are major concerns, treatment may be considered regardless of patient perceptions.[23]

Treatment of the patient with OAB involves patient education and behavioral modification as first-line therapy. Pharmacologic treatment with an antimuscarinic or, more recently, with mirabegron, is often used in combination with behavioral intervention to maximize treatment benefit. For patients who are intolerant of or fail pharmacologic therapy from an efficacy standpoint, intradetrusor injection of onabotulinumtoxinA and neuromodulation are available. Neuromodulation using sacral nerve stimulation or posterior tibial nerve stimulation is approved for the treatment of OAB, but will not be discussed in this article.

Patient education is a cornerstone of effective treatment of OAB.[23] Understanding normal bladder control provides a comparator for assessing the patient's own treatment progress and setting realistic expectations for symptom control (eg, understanding that most OAB treatments can improve symptoms but not eliminate them) likely contributes to better treatment adherence and outcome satisfaction.[21,23] Often, setting task-oriented goals (eg, being able to sit through a movie uninterrupted if that is not currently possible due to symptoms) instead of number-oriented goals (eg, reducing number of incontinence episodes per day from 6 to 3) is more motivating for patients. Understanding the benefits vs risks/burdens of available treatment options is also important for informed decision making.

First-line treatment for OAB is behavioral modification (eg, bladder training, bladder control strategies, pelvic floor muscle training, fluid management, lifestyle changes such as weight loss, dietary changes).[23] Patient education resources may be found at:

- http://www.auanet.org/common/pdf/products/OABPatientGuide.pdf
- http://www.kidney.niddk.nih.gov/kudiseases/pubs/uiwomen/#treatment
- http://c.ymcdn.com/sites/www.iuga.org/resource/resmgr/brochures/eng_btraining.pdf

Typical mean improvements from behavioral modification are comparable to pharmacologic treatment and range from 50% to 80% reduction in frequency of urinary incontinence.[23,24] For patients who have an inadequate response to behavioral therapy, the addition of drug therapy can improve symptom control and QOL.[23,25,26] Given that many patients do not seek medical care until their symptoms become intolerable, combination therapy to provide faster relief may be particularly beneficial in many cases.

CASE STUDY #1 (*continued*): Sally returns after 2 months of following a behavioral modification plan and reports, "I'm getting some relief of symptoms, but I'm still concerned that I'm going to have to wear a diaper during the ceremony. The wedding is in 2 months. Is there anything else we can do to help me gain better control of my bladder?"

CONSIDERATIONS IN PHARMACOLOGIC MANAGEMENT AS SECOND-LINE THERAPY

Antimuscarinic therapy is the gold standard for pharmacologic treatment of OAB and is often used in combination with behavioral therapy.[23] Several antimuscarinic agents are now available which vary in their muscarinic receptor affinity, formulation, and dose flexibility (**TABLE 1**).[7,27-33] All antimuscarinics are effective for OAB, with differences in their muscarinic receptor affinities possibly leading to differences in tolerability profiles.[34] It is generally felt that if a patient experiences inadequate symptom control and/or unacceptable adverse effects with 1 of the antimuscarinic agents, another may be tried.[23,35]

Discontinuation rates of 80% to 90% within the first year of therapy have been reported for antimuscarinic agents used for OAB, with 1 study reporting a median of 31 days to discontinuation.[21,36] A primary reason for the discontinuation of these agents is the burden of anticholinergic side effects such as somnolence, blurred vision, and particularly dry mouth and constipation.[23] Anticholinergic side effects are of particular concern in the elderly. Clinicians can help mitigate these discontinuation rates by reviewing the patient's medication list to identify other medications that might potentiate anticholinergic side effects, as well as by educating patients about the likely side effects and steps to take to avoid or minimize their occurrence.

For example, patients should be educated about dry mouth and advised to use sugar-free hard candies, chewing gum, or oral lubricants. Similarly, patients should be educated about the risk of constipation and the importance of adequate fluid intake, dietary fiber and fiber supplements, and normal bowel habits.[23] At each visit, clinicians should

TABLE 1 **Characteristics of pharmacologic agents for treatment of overactive bladder**[7,27-33]

Drug	Dose range	Dosage form	Metabolism	Receptor affinity	Other notes
Darifenacin (Enablex)	7.5–15 mg once daily	Tablet, ER	Hepatic by CYP450 isoforms	M3	Low rate of CNS side effects; high rate of constipation (14.8% to 21.3%)
Fesoterodine (Toviaz)	4–8 mg once daily	Tablet, ER	Hepatic by CYP450 isoforms	M1, M2, M3, M5	Low CNS penetration; possibly fewer CNS side effects
Oxybutynin IR (Ditropan) ER (Ditropan XL)	 5 mg 2-3 times/ day, max 4 times/ day (IR) 5-30 mg once daily (ER)	Tablet Tablet, ER	Hepatic by CYP450 isoforms	M1, M2, M3, M4	IR is limited by high rates of dry mouth; ER associated with cognitive impairment
Oxybutynin transdermal patch (Oxytrol) Oxybutynin transdermal gel (Gelnique) 3% and 10%	1 patch applied twice weekly Applied once daily	Transdermal patch Transdermal gel	Hepatic by CYP450 isoforms; second pass	M1, M2, M3, M4	Transdermal patch and gel associated with lower rates of dry mouth; transdermal patch associated with significant rate of skin reaction (lower with gel)
Solifenacin (VESIcare)	5–10 mg once daily	Tablet	Hepatic by CYP450 isoforms	M3	High rate of dry mouth at 10 mg dose (27.6% vs 10.9% at 5 mg)
Tolterodine LA (Detrol LA)	2–4 mg once daily	Capsule, ER	Hepatic by CYP450 isoforms	M1, M2, M3, M5	Constipation
Trospium (Sanctura; Sanctura XR)	20 mg twice daily (non-XR) 60 mg in the morning (XR)	Tablet	Active renal tubular secretion; no CYP450 involvement	M1, M2, M3, M4, M5	Low penetration across blood-brain barrier (quaternary amine); XR formulation should be taken in the morning
Mirabegron (Myrbetriq)	25–50 mg once daily	Tablet, ER	Multiple hepatic pathways, including CYP450 isoforms (specifically CYP2D6, though to a limited extent)	Beta-3 adrenergic receptor	Incidence of dry mouth, HTN similar to placebo; no significant CV, QT interval effects. Monitor BP, especially in HTN patients; avoid in patients with severe uncontrolled HTN. Monitor with concomitant digoxin or CYP2D6 substrates

Abbreviations: BP, blood pressure; CNS, central nervous system; CV, cardiovascular; ER, extended-release; HTN, hypertension; IR, immediate-release; LA, long-acting; M, muscarinic receptor.

inquire about these and other side effects the patient may be experiencing. If side effects to 1 antimuscarinic are intolerable despite intervention, switching to an alternative formulation or another antimuscarinic should be tried. For example, compared with immediate-release oxybutynin, the extended-release (ER) and transdermal oxybutynin formulations are associated with lower rates of dry mouth.[23]

Antimuscarinics are contraindicated in patients with narrow angle glaucoma, impaired gastric emptying, or a history of urinary retention; caution is recommended even in patients with treated narrow angle glaucoma.[23] The use of an antimuscarinic has not been evaluated in patients with myasthenia gravis and thus caution is recommended. Similarly, caution is advised in patients taking oral solid dose forms of potassium chloride because reduced gastric emptying may potentially increase potassium absorption.[23] Antimuscarinic agents may adversely affect cognitive function and should be used cautiously in the elderly and other higher risk populations.[23]

Data regarding possible cardiac adverse effects of various antimuscarinics (ie, increased heart rate and QT interval prolongation [the latter via a mechanism unrelated to muscarinic blockade]) are limited and vary among the agents.[37] Heart rate is modulated by the M2 receptor; thus, agents with a greater affinity for the M2 receptor may have a greater effect on heart rate. However, data to determine clinical relevance is lacking.[37] Most of the very limited data on QT interval prolongation with antimuscarinic agents indicate no significant effect, but since thorough studies have not been performed with all agents, increased risk with some of them cannot be excluded.[37]

Differences exist among individual agents in their adverse event profiles, pharmacokinetic profiles, muscarinic receptor specificity, and available dose formulations. Therefore, selection of antimuscarinic therapy for a particular patient depends on patient-specific factors such as comorbidities, concomitant medications, history of antimuscarinic use, cost and/or insurance reimbursement for various medications, and adverse events with previous antimuscarinic therapy.[29]

Mirabegron

An alternative to antimuscarinic therapy, mirabegron is a once-daily beta-3 adrenoreceptor agonist recently approved by the US Food and Drug Administration (FDA) for OAB. Stimulation of the beta-3 adrenoreceptor relaxes detrusor smooth muscle, decreases afferent signaling from the bladder, improves bladder compliance upon filling, and increases bladder capacity with no change in micturition pressure and residual volume.[38,39] Its unique mechanism of action provides an alternative therapy for patients as a second line therapy for OAB, particularly in patients in whom contraindications exist to the use of antimuscarinic agents and/or those intolerant to antimuscarinic agents. The potential role of combination therapy with an antimuscarinic agent and mirabegron in OAB is currently under study.[40]

As monotherapy, the efficacy and tolerability of mirabegron have been demonstrated in phase II trials, in 3 pivotal, large-scale phase III multinational, randomized, controlled trials for up to 12 weeks (assessing 25 mg once daily and/or 50 mg once daily), and in 1 phase III study assessing 12-month safety and efficacy.[38,41-43] In a phase III trial, mirabegron 25 mg once daily demonstrated greater mean decreases from baseline vs placebo for incontinence episodes (–1.36 vs. –0.96; $P = .005$) and micturitions (–1.65 vs. –1.18; $P = .007$) per 24 hours.[42] In a head-to-head comparison, both mirabegron 50 or 100 mg/day and tolterodine ER 4 mg/day improved key OAB symptoms from the first measured time point of 4 weeks and maintained efficacy throughout the 12-month treatment period.[43]

A pooled safety analysis of the three 12-week phase III studies yielded similar overall incidences of adverse effects in mirabegron (25-100 mg/day), placebo, and tolterodine ER 4 mg/day groups.[44] The most common drug-related adverse events in the mirabegron groups were hypertension (3.4% to 6.9%, not dose-related) and headache (0.9% to 2.0%, not dose-related), which were similar in incidence to placebo and tolterodine ER; and dry mouth, which was similar between the mirabegron (0.9% to 2.2%, not dose-related) and placebo (1.6%) groups, but of a higher incidence in the tolterodine ER group (9.5%). There were no significant cardiovascular events and no effects on the QT interval in the mirabegron groups. In healthy volunteers, mirabegron has not shown an association with QT prolongation at the 50 mg or 100 mg doses, but did so at the 200 mg dose in females.[45] Mirabegron increased heart rate in these subjects in a dose-dependent manner (6.7, 11, and 17 beats per minute mean increase from baseline for the 50, 100, and 200 mg doses, respectively).[32,45] In this and another healthy volunteer study, mirabegron was also associated with dose-dependent increases in systolic blood pressure (3.0, 5.5, and 9.7 mm Hg in 1 study and 2.5, 4.5, and 6.5 mm Hg in another study for 50, 100, and 200 mg doses, respectively).[32]

Given its side effect profile, mirabegron may be particularly useful for patients in whom antimuscarinic-associated dry mouth is intolerable, but may be used in antimuscarinic naive patients also (**TABLE 1**). Periodic blood pressure determinations, especially in hypertensive patients, are recommended. Mirabegron should be avoided in patients with severe, uncontrolled hypertension.[32]

CASE STUDY #1 (*continued*): Sally's primary care provider discusses adding antimuscarinic therapy to her behavior management therapy, to which Sally readily agrees. Sally is educated about common anticholinergic side effects and is advised to avoid driving shortly after taking a dose and to check with her primary care provider or pharmacist before starting any new medications (including nonprescription medications). She is also educated about steps to take to minimize dry mouth and constipation. A follow-up visit is scheduled prior to the wedding.

CASE STUDY #2: Mildred, a 69-year-old patient who has been taking tolterodine ER for OAB for 4 months, returns for follow-up and reports: "These pills don't work and they make my mouth dry. I take so many medications, I don't want another pill. I've given up coffee, tea, and chocolate and my symptoms are no better. What else can be done to control my bladder symptoms? I don't like the idea of a permanent device in my body."

INTRADETRUSOR INJECTION OF ONABOTULINUMTOXINA

Intradetrusor injection of onabotulinumtoxinA, approved by the FDA in January 2013 for patients with OAB, inhibits the neuronal release of acetylcholine, the neurotransmitter involved in detrusor overactivity.[46] Intradetrusor onabotulinumtoxinA is considered a third-line treatment that may be offered to carefully selected and thoroughly counseled patients who have failed treatment with antimuscarinic therapy (from either an efficacy or tolerability standpoint). Patients must be able and willing to return for frequent postvoid residual (PVR) evaluation and to perform self-catheterization if necessary.[23]

TABLE 2 Selected clinical trials of onabotulinumtoxinA in idiopathic overactive bladder

Study description	Previous therapy	Treatment arms	Efficacy outcomes	Safety outcomes
Nitti et al[48] R, DB, PC, phase III Duration: 24 wks Baseline (mean) episodes: UI, 5.1–5.5/d UUI, 4.5–4.8/d micturition, 11.2–12.0/d urgency, 7.9–8.5/d nocturia, 2.0–2.2/d PVR, 25–27.8 mL I-QOL, total summary score, 36.5–37.3	Anticholinergics: mean duration 2.3–2.6 y; mean number 2.4–2.5	OnabotulinumtoxinA 100 units x 1 with repeat treatment any time after 12 wks at patient request if they had ≥2 UUI episodes during 3 d (n = 280) vs Placebo (n = 277)	Change from baseline at 12 wks: Micturitions/d, –2.15 vs –0.91[a] UI episodes/d, –2.65 vs –0.87[a] Urgency episodes/d, –2.93 vs –1.21[a] Nocturia episodes/d, –0.45 vs –0.24[b] Vol voided/micturition, 41.1 vs 9.7 mL[a] I-QOL total summary score, 21.9 vs 6.8[a]	At 12 wks (%): UTIs, 15.5 vs 5.9 Dysuria, 12.2 vs 9.6 Bacteriuria, 5.0 vs 5.8 UR,[c] 5.4 vs 0.4
Chapple et al[49] R, DB, PC, phase III Duration: 12 wks Baseline (mean) episodes: UI, 5.5–5.7/d; UUI 5.1–5.2/d; micturition, 11.8–12.0/d; urgency, 8.8–9.1/d; nocturia, 2.1–2.2/d; PVR, 13.8–17.2 mL	Anticholinergics: mean duration 2.1–2.2 y; mean number 2.3–2.5	OnabotulinumtoxinA 100 units x 1 (n = 277) vs Placebo (n = 271)	Change from baseline at 12 wks: Micturitions/d, –2.56 vs –0.83[d] UI episodes/d, –2.95 vs –1.03[a] Urgency episodes/d, –3.67 vs –1.24[d] Nocturia episodes/d, –0.54 vs –0.25[d] UUI episodes/d, –2.80 vs –0.82[d] KHQ - proportion improved or greatly improved on treatment benefit scale: 62.8 vs 26.8[a]	At 12 wks (%): UTIs, 20.4 vs 5.2 Dysuria, 5.8 vs 3.7 Bacteriuria, 3.6 vs 2.2 UR, 5.8 vs 0.4 CIC,[e] 6.9 vs 0.7
Dmochowski et al[50] R, DB, PC, phase II dose ranging study (50 U, 100 U, 150 U, 200 U, 300 U)[f] Duration: 36 wks Baseline: ≥8 UUI episodes/wk ≥8 micturitions/d	Anticholinergics	OnabotulinumtoxinA 100 units x 1 (n = 54) vs Placebo (n = 44)	Change from baseline at 12 wks: UUI episodes/wk, –18.4 vs –17.4	At 36 wks (%): UTIs, 36.4 vs 16.3 UR, 18.2 vs 2.3 CIC, 10.9 vs 0

Abbreviations: AE, adverse event; CIC, clean intermittent catheterization; d, day; DB, double-blind; I-QOL, incontinence quality of life; KHQ, King's Health Questionnaire; PC, placebo-controlled; PVR, postvoid residual urine volume; R, randomized; UI, urinary incontinence; UR, urinary retention; UTI, urinary tract infection; UUI, urinary urgency incontinence; wk, week; y, year.

[a]$P < 0.001$ vs placebo.

[b]$P \leq .05$ vs placebo.

[c]PVR ≥200 mL requiring CIC.

[d]$P < .01$ vs placebo.

[e]Indications for CIC: PVR≥350 mL or PVR 200-350 mL with symptoms.

[f]Only onabotulinumtoxinA 100-unit arm results reported here.

Administration of intradetrusor onabotulinumtoxinA is a minimally invasive procedure that may be done in the office or in the operating room under IV sedation, depending on patient-specific factors. It involves injection (100 units/10 mL via 20 injections of 0.5 mL each) into the detrusor muscle via flexible or rigid cystoscope.[46,47] Patients should be considered for reinjection when the clinical effect has diminished (median time in clinical trials was 169 days) but no sooner than 12 weeks from the prior bladder injection.[46] Since the total dose that can be administered over a 3-month period is 360 units for all indications combined, it is important to determine if the patient has received onabotulinumtoxinA for any other indications, or is planning to, during the months before and after administration for OAB.[46]

Several randomized, controlled clinical trials have demonstrated the efficacy of onabotulinumtoxinA in decreasing incontinence episodes, frequency, and urgency, and in improving QOL (**TABLE 2**).[48-50] The 2- to 4-fold improvement over placebo in all symptoms of OAB observed in clinical trials of onabotulinumtoxinA 100 units is noteworthy, as an effect of this magnitude does not seem to have been reported with antimuscarinics or mirabegron.[51]

Uncomplicated urinary tract infection (UTI) was the most frequently reported adverse event observed with onabotulinumtoxinA in clinical trials.[48,49] A significant increase in the PVR volume was also seen, requiring clean intermittent catheterization in 6.1% to 6.9% of patients. Clean intermittent catheterization was initiated if PVR ≥200 mL; <350 mL with associated symptoms; or ≥350 mL, regardless of symptoms. Discontinuation rates due to adverse effects were approximately 1% at 12 weeks in the 2 trials.

Due to the limited diffusion and localized injections of onabotulinumtoxinA, the likelihood of systemic side effects is very low. However, there are postmarketing reports of symptoms occurring hours to weeks after injection: asthenia, generalized muscle weakness, diplopia, ptosis, dysphagia, dysphonia, dysarthria, urinary incontinence, and breathing difficulties.[46] Although the risk is likely greatest in children treated for spasticity as opposed to adults treated for OAB or other indications, OAB patients should be counseled accordingly.

CASE STUDY #2 (*continued*): The primary care provider discusses the benefits and limitations of the transdermal patch and gel formulations of oxybutynin and of intradetrusor injection of onabotulinumtoxinA. Since side effects may be less bothersome with oxybutynin transdermal patch and it is available without a prescription, Mildred agrees to try it for a month.

A month later, Mildred returns and reports that her symptoms are minimally improved. She is noted to have significant skin irritation at the site of administration. Mildred and her primary care provider discuss onabotulinumtoxinA and agree that she should be referred to a urologist.

CONSIDERATIONS FOR REFERRAL

While most patients with OAB can be managed in the primary care setting, several situations warrant consideration for referral to a specialist. These include physician uncertainty regarding the diagnosis, obstructive voiding symptoms (eg, sensation of incomplete emptying, straining to void), significant pelvic organ prolapse, prior pelvic surgery or radiation, hematuria, recurrent UTIs, or comorbid neurologic conditions that may affect bladder function (eg, stroke, multiple sclerosis, spinal cord injury).[23] In addition, patients who have failed adequate trials of antimuscarinic or mirabegron therapy should be considered for referral to a urologist or urogynecologist for intradetrusor injection of onabotulinumtoxinA or neuromodulation.

CONCLUSION

Overactive bladder is a common symptom complex that has a considerable negative impact on health and QOL, yet still remains underdiagnosed and undertreated. A history, focused physical examination (abdominal, pelvic, neurologic), and urinalysis is often all that is needed for evaluation. While patient education and behavioral modification are the cornerstones of treatment, several new treatment options provide for greater opportunity for individualized pharmacologic management in primary care. For those refractory to or intolerant of pharmacologic therapy, intradetrusor injection of onabotulinumtoxinA is a new option. ●

REFERENCES

1. Yoshida M, Masunaga K, Nagata T, Yono M, Homma Y. The forefront for novel therapeutic agents based on the pathophysiology of lower urinary tract dysfunction: pathophysiology and pharmacotherapy of overactive bladder. *J Pharmacol Sci*. 2010;112(2):128-134.
2. Milsom I, Abrams P, Cardozo L, Roberts RG, Thüroff J, Wein AJ. How widespread are the symptoms of an overactive bladder and how are they managed? A population-based prevalence study [published correction appears in *BJU Int*. 2001;88(7):807]. *BJU Int*. 2001;87(9):760-766.
3. Byles J, Millar CJ, Sibbritt DW, Chiarelli P. Living with urinary incontinence: a longitudinal study of older women. *Age Ageing*. 2009;38(3):333-338; discussion 251.
4. Palleschi G, Pastore AL, Maggioni C, et al. Overactive bladder in diabetes mellitus patients: a questionnaire-based observational investigation [published online ahead of print October 8, 2013]. *World J Urol*. 2013;doi: 10.1007/s00345-013-1175-3.
5. Chiu AF, Huang MH, Wang CC, Kuo HC. Higher glycosylated hemoglobin levels increase the risk of overactive bladder syndrome in patients with type 2 diabetes mellitus. *Int J Urol*. 2012;19(11):995-1001.
6. Stewart WF, Van Rooyen JB, Cundiff GW, et al. Prevalence and burden of overactive bladder in the United States. *World J Urol*. 2003;20(6):327-336.
7. Rosenberg MT, Newman DK, Tallman CT, Page SA. Overactive bladder: recognition requires vigilance for symptoms. *Cleve Clin J Med*. 2007;74(suppl 3):S21-S29.
8. Onukwugha E, Zuckerman IH, McNally D, Coyne KS, Vats V, Mullins CD. The total economic burden of overactive bladder in the United States: a disease-specific approach. *Am J Manag Care*. 2009;15(4 suppl):S90-S97.
9. Ricci JA, Baggish JS, Hunt TL, et al. Coping strategies and health care-seeking behavior in a US national sample of adults with symptoms suggestive of overactive bladder. *Clin Ther*. 2001;23(8):1245-1259.
10. Helfand BT, Evans RM, McVary KT. A comparison of the frequencies of medical therapies for overactive bladder in men and women: analysis of more than 7.2 million aging patients. *Eur Urol*. 2010;57(4):586-591.
11. Tubaro A. Defining overactive bladder: epidemiology and burden of disease. *Urology*. 2004;64(6 suppl 1):2-6.
12. Coyne KS, Sexton CC, Irwin DE, Kopp ZS, Kelleher CJ, Milsom I. The impact of overactive bladder, incontinence and other lower urinary tract symptoms on quality of life, work productivity, sexuality and emotional well-being in men and women: results from the EPIC study. *BJU Int*. 2008;101(11):1388-1395.
13. Milsom I, Kaplan SA, Coyne KS, Sexton CC, Kopp ZS. Effect of bothersome overactive bladder symptoms on health-related quality of life, anxiety, depression, and treatment seeking in the United States: results from EpiLUTS. *Urology*. 2012;80(1):90-96.
14. Darkow T, Fontes CL, Williamson TE. Costs associated with the management of overactive bladder and related comorbidities. *Pharmacotherapy*. 2005;25(4):511-519.
15. Brown JS, Vittinghoff E, Wyman JF, et al. Urinary incontinence: does it increase risk for falls and fractures? Study of Osteoporotic Fractures Research Group. *J Am Geriatr Soc*. 2000;48(7):721-725.
16. Morrison A, Levy R. Fraction of nursing home admissions attributable to urinary incontinence. *Value Health*. 2006;9(4):272-274.

17. Kinchen KS, Burgio K, Diokno AC, Fultz NH, Bump R, Obenchain R. Factors associated with women's decisions to seek treatment for urinary incontinence. *J Womens Health (Larchmt)*. 2003;12(7):687-698.
18. Minassian VA, Yan X, Lichtenfeld MJ, Sun H, Stewart WF. Predictors of care seeking in women with urinary incontinence. *Neurourol Urodyn*. 2012;31(4):470-474.
19. Goepel M, Hoffmann JA, Piro M, Rübben H, Michel MC. Prevalence and physician awareness of symptoms of urinary bladder dysfunction. *Eur Urol*. 2002;41(3):234-239.
20. Dmochowski RR, Newman DK. Impact of overactive bladder on women in the United States: results of a national survey. *Curr Med Res Opin*. 2007;23(1):65-76.
21. Schabert VF, Bavendam T, Goldberg EL, Trocio JN, Brubaker L. Challenges for managing overactive bladder and guidance for patient support. *Am J Manag Care*. 2009;15 (4 suppl):S118-S122.
22. Drutz HP. Overactive bladder: the importance of tailoring treatment to the individual patient. *J Multidiscip Healthc*. 2011;4:233-237.
23. Gormley EA, Lightner DJ, Burgio KL, et al; American Urological Association; Society of Urodynamics, Female Pelvic Medicine & Urogenital Reconstruction. Diagnosis and treatment of overactive bladder (non-neurogenic) in adults: AUA/SUFU guideline. *J Urol*. 2012;188(6 suppl):2455-2463.
24. Burgio KL, Locher JL, Goode PS, et al. Behavioral vs drug treatment for urge urinary incontinence in older women: a randomized controlled trial. *JAMA*. 1998;280(23):1995-2000.
25. Rai BP, Cody JD, Alhasso A, Stewart L. Anticholinergic drugs versus non-drug active therapies for non-neurogenic overactive bladder syndrome in adults. *Cochrane Database Syst Rev*. 2012;12:CD003193.
26. Burgio KL, Locher JL, Goode PS. Combined behavioral and drug therapy for urge incontinence in older women. *J Am Geriatr Soc*. 2000;48(4):370-374.
27. Jamshidi R, Moore A, Park A, et al; Association of Reproductive Health Professionals. Diagnosis and management of overactive bladder. A quick reference guide for clinicians. http://www.arhp.org/uploadDocs/OABQRG.pdf. Published 2011. Accessed January 2, 2014.
28. Callegari E, Malhotra B, Bungay PJ, et al. A comprehensive non-clinical evaluation of the CNS penetration potential of antimuscarinic agents for the treatment of overactive bladder. *Br J Clin Pharmacol*. 2011;72(2):235-246.
29. Bettez M, Tu le M, Carlson K, et al. 2012 update: guidelines for adult urinary incontinence collaborative consensus document for the canadian urological association. *Can Urol Assoc J*. 2012;6(5):354-363.
30. Enablex [package insert]. Rockaway, NJ: Warner Chilcott (US), LLC; 2013.
31. VESIcare [package insert]. Northbrook, IL: Astellas Pharma US, Inc.; 2013.
32. Myrbetriq [package insert]. Northbrook, IL: Astellas Pharma US, Inc.; 2012.
33. Oxybutynin [package insert]. Livonia, MI: Major Pharmaceuticals; 2012.
34. Chapple C, Khullar V, Gabriel Z, Dooley JA. The effects of antimuscarinic treatments in overactive bladder: a systematic review and meta-analysis [published correction appears in *Eur Urol*. 2005;48(5):875]. *Eur Urol*. 2005;48(1):5-26.
35. Madhuvrata P, Cody JD, Ellis G, Herbison GP, Hay-Smith EJ. Which anticholinergic drug for overactive bladder symptoms in adults. Cochrane Database Syst Rev. 2012;1:CD005429.
36. D'Souza AO, Smith MJ, Miller LA, Doyle J, Ariely R. Persistence, adherence, and switch rates among extended-release and immediate-release overactive bladder medications in a regional managed care plan. *J Manag Care Pharm*. 2008;14(3):291-301.
37. Andersson KE, Campeau L, Olshansky B. Cardiac effects of muscarinic receptor antagonists used for voiding dysfunction. *Br J Clin Pharmacol*. 2011;72(2):186-196.
38. Andersson KE, Martin N, Nitti V. Selective β_3-adrenoceptor agonists for the treatment of overactive bladder. *J Urol*. 2013;190(4):1173-1180.
39. Sacco E, Bientinesi R. Mirabegron: a review of recent data and its prospects in the management of overactive bladder. *Ther Adv Urol*. 2012;4(6):315-324.
40. Abrams P, Kelleher C, Staskin D, et al. Combination treatment with mirabegron and solifenacin in patients with overactive bladder (OAB)—efficacy results from a phase 2 study (Symphony). Paper presented at: American Urological Association Annual Meeting; May 4-8, 2013; San Diego, CA.
41. Khullar V, Amarenco G, Angulo JC, et al. Efficacy and tolerability of mirabegron, a β(3)-adrenoceptor agonist, in patients with overactive bladder: results from a randomised European-Australian phase 3 trial. *Eur Urol*. 2013;63(2):283-295.
42. van Kerrebroeck P, Barkin J, Castro-Diaz D, et al. Randomised, double-blind, placebo-controlled phase III study to assess the efficacy and safety of mirabegron 25 mg and 50 mg once-daily in overactive bladder (OAB). Paper presented at: 42nd Annual Meeting of the International Continence Society; October 15-19, 2012; Beijing, China.
43. Chapple CR, Kaplan SA, Mitcheson D, et al. Randomized double-blind, active-controlled phase 3 study to assess 12-month safety and efficacy of mirabegron, a β(3)-adrenoceptor agonist, in overactive bladder. *Eur Urol*. 2013;63(2):296-305.
44. Nitti VW, Khullar V, Van Karrebroeck P et al. Mirabegron for the treatment of overactive bladder: a prespecified pooled efficacy analysis and pooled safety analysis of three randomised, double-blind, placebo-controlled, phase III studies. *Int J Clin Pract*. 2013;67(7):619-632.
45. Malik M, van Gelderen EM, Lee JH, et al. Proarrhythmic safety of repeat doses of mirabegron in healthy subjects: a randomized, double-blind, placebo-, and active-controlled thorough QT study. *Clin Pharmacol Ther*. 2012;92(6):696-706.
46. Botox [package insert]. Irvine, CA: Allergan, Inc.; 2013.
47. Orasanu B, Mahajan ST. The use of botulinum toxin for the treatment of overactive bladder syndrome. *Indian J Urol*. 2013;29(1):2-11.
48. Nitti VW, Dmochowski R, Herschorn S, et al; EMBARK Study Group. OnabotulinumtoxinA for the treatment of patients with overactive bladder and urinary incontinence: results of a phase 3, randomized, placebo controlled trial. *J Urol*. 2013;189(6):2186-2193.
49. Chapple C, Sievert KD, MacDiarmid S, et al. OnabotulinumtoxinA 100 U significantly improves all idiopathic overactive bladder symptoms and quality of life in patients with overactive bladder and urinary incontinence: a randomised, double-blind, placebo-controlled trial. *Eur Urol*. 2013;64(2):249-256.
50. Dmochowski R, Chapple C, Nitti VW, et al. Efficacy and safety of onabotulinumtoxinA for idiopathic overactive bladder: a double-blind, placebo controlled, randomized, dose ranging trial. *J Urol*. 2010;184(6):2416-2422.
51. Andersson KE. New developments in the management of overactive bladder: focus on mirabegron and onabotulinumtoxinA. *Ther Clin Risk Manag*. 2013;9:161-170.

Chronic Migraine in Women

Roger K. Cady, MD

CONTINUING MEDICAL EDUCATION

LEARNING OBJECTIVES

After reading this article, the family physician will be able to:

1. Differentiate the clinical features and common comorbidities of chronic versus episodic migraine in women
2. Describe techniques to better assess migraine-related disability
3. Identify women with chronic migraine who are candidates for preventive therapy
4. Describe the efficacy and safety of pharmacologic options for abortive therapy
5. Describe the efficacy and safety of pharmacologic options for preventive therapy

TARGET AUDIENCE

Family physicians and clinicians who wish to gain increased knowledge and greater competency regarding primary care management of chronic migraine in women.

DISCLOSURES

As a continuing medical education provider accredited by the Accreditation Council for Continuing Medical Education (ACCME), it is the policy of Primary Care Education Consortium (PCEC) to require any individual in a position to influence educational content to disclose the existence of any financial interest or other personal relationship with the manufacturer(s) of any commercial product(s).

Roger K. Cady, MD discloses that he is on the advisory boards for Allergan, Inc.; Avanir Pharmaceuticals, Inc.; and Zogenix, Inc. He is on the speakers' bureau for NuPathe Inc.

Allan J. Wilke MD, CME reviewer, discloses that he has no real or apparent conflicts of interest to report.

Gregory Scott, PharmD, RPh, medical writer, discloses that he has no real or apparent conflicts of interest to report.

CONFLICTS OF INTEREST

When individuals in a position to control content have reported financial relationships with one or more commercial interests, Primary Care Education Consortium works with them to resolve such conflicts to ensure that the content presented is free of commercial bias. The content of this activity was vetted by the following mechanisms and modified as required to meet this standard:

- Content peer review by an external topic expert
- Content peer review by an external CME reviewer
- Content validation by internal Primary Care Education Consortium clinical editorial staff

OFF-LABEL DISCLOSURES

In accordance with ACCME guidelines, the faculty author has been asked to disclose discussion of unlabeled or unapproved uses of drugs or devices during the course of the activity.

SPONSORSHIP

This activity is sponsored by Primary Care Education Consortium and Primary Care Metabolic Group.

ACCREDITATION

This activity has been planned and implemented in accordance with the Essential Areas and policies of the Accreditation Council for Continuing Medical Education (ACCME) and Primary Care Education Consortium. Primary Care Education Consortium is accredited by the ACCME to provide continuing medical education to physicians.

AMA PRA CATEGORY 1

Primary Care Education Consortium designates this activity, "Chronic Migraine in Women," for a maximum of 1.0 AMA PRA Category 1 Credit ™. Physicians should claim only the credit commensurate with the extent of their participation in the activity.

Release Date: February 1, 2014
Expiration Date: January 31, 2015

METHOD OF PARTICIPATION

PHYSICIANS
To receive CME credit, please read the journal article and on completion, go to www.pceconsortium.org/migraine to complete the online post-test and receive your certificate of completion.

PHYSICIAN ASSISTANTS
AAPA accepts certificates of participation of educational activities certified for AMA PRA Category 1 Credit™ from organizations accredited by ACCME or a recognized state medical society.

SUPPORTER

This activity was supported by an educational grant from Allergan, Inc.

INTRODUCTION

Primary headache disorders are the fifth leading cause of disability for women worldwide.[1] The annual prevalence of migraine in the United States is 18% for adult women and the lifetime prevalence is estimated to be 26%.[2] In women, the prevalence of chronic migraine (CM) is more than twofold higher than in men.[3] Chronic migraine is and should be considered a complication of episodic migraine (EM) that extracts a significant human and social burden from those living with this condition. This is particularly true for women, since they experience a greater disease burden as demonstrated by greater headache-related disability and reduced productivity relative to men.[3,4]

While 70% of the migraine population is managed in a primary care setting, it is estimated that a quarter are dissatisfied or very dissatisfied with their care.[5] To a significant degree, this is due to a failure to adequately treat EM and institute effective preventive measures early to halt the progression of EM to CM.[6]

CASE STUDY: Rita is a 38-year-old woman who was diagnosed 12 years ago with migraine without aura. Her migraines responded to naproxen sodium until several years ago, at which time she was prescribed a triptan. Over the past 12 to 18 months, Rita has increasingly observed that her response to triptan therapy has been less robust, noting recurring headache within 1 to 2 days following triptan therapy. This mandated an additional dose of her triptan and naproxen sodium. When the headache is particularly debilitating, she also supplements her treatment with an over-the-counter headache combination product. Review of her headache diary shows that Rita now experiences 3 to 4 migraines fulfilling International Headache Society (IHS) criteria[7] per month, but with headache of moderate to severe intensity occurring on 12 to 15 days per month. She was prescribed topiramate 1 year ago, but it was discontinued because she experienced cognitive changes as the dose was increased.

The increasing frequency of Rita's migraine headaches and the growing lack of response to naproxen sodium and triptan therapy indicate that her diagnosis should be reevaluated and other possible contributory causes should be investigated. In addition, the subtype of migraine and treatment plan should be reassessed.

DIFFERENTIATING EPISODIC MIGRAINE FROM CHRONIC MIGRAINE

It has only been within the past few years that consensus-based criteria for CM have become established and the clinical features of CM have been recognized. It was not until 2004 that a formal definition of CM was adopted by the IHS, with further refinement in 2005.[7,8] It should be made clear that other terms, such as chronic daily headache, transformed migraine, and medication overuse headache (MOH), are not synonymous with CM. The recognition of CM as a migraine subtype, along with EM, underscored the clinical importance of CM.

Episodic migraine

Episodic migraine is characterized by headache features that include unilateral location, pulsating quality, moderate or severe intensity, and aggravation by routine physical activity (**TABLE**). Nonheadache associated features include nausea and/or photophobia and phonophobia. Episodic migraine can be divided into migraine with or without aura. While many patients experience both, approximately 30% of migraines are associated with aura occurring prior to or during the headache phase of the attack.[9] Auras are considered a consequence of an electrical event in the brain called spreading cortical depression and consist of fully reversible focal neurological symptoms that are visual or sensory in nature. More importantly, EM is characterized by a return to normal baseline neurological function between each episode.

Chronic migraine

Chronic migraine often follows years after the onset of EM, and because of that, CM can be considered a complication of EM.[7] As headache frequency increases, migraines begin to lose their episodic nature and there is little or no time for neurological recovery between headaches.[10] Consequently, symptoms and disability are variable. This often leads to diagnostic uncertainty since patients typically report to their health care provider only their worst headache days as being migraine. Because the stereotypic nature of migraine observed in EM is less clear in CM, CM is measured in headache days rather than in attacks or episodes. CM is defined as ≥15 days of headache per month for more than 3 months, of which 8 or more headache days per month must fulfill the IHS criteria cited above for EM.[11] Other headache days may have features of tension-type or probable migraine and as such it is entirely possible that patients with CM experience more days with headache other than migraine than those that meet the IHS criteria for migraine.

Because the treatment need for CM is great, patients frequently overuse acute medication. This results often in another type of headache called MOH (previously called rebound headache). Medication overuse headache is particularly common with simple analgesics and triptans, as well as with caffeine, opioids, and barbiturates, although opioids and barbiturates are generally not recommended for management of EM or CM.[12]

In order to obtain an accurate understanding of headache days, it is valuable to ask patients how many days per month they are totally free of headache. The answer to this question is

Roger K. Cady, MD, Medical Director, Headache Care Center, Clinvest/a Division of Banyan Group, Inc., Springfield, MO

DISCLOSURES
Dr. Cady discloses that he is on the advisory boards for Allergan, Inc.; Avanir Pharmaceuticals, Inc.; and Zogenix, Inc. He is on the speakers' bureau for NuPathe Inc.

SUPPORT
This activity is sponsored by PCEC and is supported by an educational grant from Allergan, Inc.

TABLE Selected clinical differences between episodic and chronic migraine

Feature	Episodic migraine	Chronic migraine
Headache frequency, days/month	<15	≥15
Experience severe headache pain, %	78.1%	92.4%[a]
Duration of headache without medication, mean hours	38.8	65.1[a]
Duration of headache with medication, mean hours	12.8	24.1[a]
Age, mean years (SD)	46.0 (13.8)	47.7[a] (14.0)
Women, %	80.0	78.6
Occupationally disabled, %	11.1	20.0[a]

Abbreviation: SD, standard deviation.

[a]*P* < .05

With kind permission from Springer Science+Business Media: *Curr Pain Headache Rep*, Defining the differences between episodic migraine and chronic migraine, volume 16, 2012, page 88, Katsarava Z, Buse DC, Manack AN, Lipton RB, Table 1.

often much more revealing than the number of migraine episodes per month.[12,13]

Relative to EM, headache-related disability is greater in CM and serves as an important issue to discuss with patients when assessing impact. However, headache-related disability can vary during a migraine attack, as well as from 1 attack to another. Results of the American Migraine Prevalence and Prevention study (N = 162,576) showed that, during a severe headache, 54% of patients with migraine experienced severe impairment or required bed rest, while 46% experienced only some or no impairment.[14]

Chronic migraine patients are less likely than patients with EM to be employed full-time, 2 to 3 times as likely to experience reduced occupational or household productivity, and 4 times as likely to experience missed family activities. The risk of anxiety, chronic pain, or depression is almost twice as high in patients with CM as with EM.[13,15,16] In addition, patients with CM have a 50% to 70% higher risk of asthma or chronic obstructive pulmonary disease, a 40% higher risk of heart disease and angina, and a 65% higher risk of stroke than patients with EM.[13] Compared with patients with EM, those with CM are more likely to have visited a primary care physician within the past 3 months (13.9% vs 26.2%; $P < .001$) and have higher total mean headache-related costs during a 3-month period ($383 vs $1036; $P < .001$).[17] These factors underscore the importance and value of a primary care physician's involvement in managing the patient with migraine.

Several risk factors for development of CM have been identified. These include frequent EM, poor response to acute migraine treatment, major stressors, depression, anxiety, snoring and sleep apnea, obesity, and overuse of acute treatment medications.[18,19] There are also associated nonmodifiable risk factors such as older age, female gender, Caucasian race, low educational level/socioeconomic status, and head injury.[12,13]

CASE STUDY (*continued*): Upon further questioning by her primary care physician, Rita states that she has only 4 or 5 days per month where she is truly headache-free. She is now using some form of acute medication 4 or 5 days per week. Rita is missing work and unable to care for her family for 24 to 36 hours during each of the 3 or 4 severe migraine attacks she experiences each month. Rita acknowledges feelings of depression and difficulty sleeping.

MANAGEMENT OF CHRONIC MIGRAINE

It must be realized that because CM was recognized as a migraine subtype only a few years ago, the comprehensive management of patients with CM is unclear. Few clinical trials of pharmacologic therapies have been conducted in patients meeting the definition of CM. Those that have been done involve preventive therapy for CM. Beyond this limited information, the management of patients with CM draws on experience treating other migraine subtypes, particularly EM, although its applicability to CM is relatively unproven.

Managing CM successfully requires patients to actively participate in decisions related to their management. As a largely self-managed chronic disease, the appropriate use (and avoidance of overuse) of medications ultimately rests with the patient. The health care provider has a critical role in therapeutic decision making and appropriate prescribing, as well as educating the patient regarding the risks of medications, including avoiding their overuse.

Another principle of management is that the focus of treatment should be on the whole patient and not solely on the

migraine episodes. Consequently, in addition to considering severity of illness, comorbidities, and prior response to medications, treatment should be individualized to include the patient's needs, preferences, and values. This underscores the central role of primary care in management of the migraine patient.

There are 4 components of treatment: patient education and support, nonpharmacologic therapy, pharmacologic therapy, and ongoing assessment. A key aspect of patient education is to discuss a patient's treatment expectations in order to create alignment in establishing realistic therapeutic goals. These goals need to be important to the patient and the time to achieve them should be realistic. A clinical benefit with preventive therapies, for example, often takes 2 to 3 months. Although not discussed in this article, incorporating appropriate nonpharmacological therapies, such as diet, sleep hygiene, exercise, and use of complementary and alternative therapies such as acupuncture, is generally helpful.[20-22]

Pharmacologic treatment of chronic migraine

The overarching goals of pharmacologic treatment for CM are to reduce the headache burden and improve functioning and quality of life, while avoiding treatment-related side effects and complications. To achieve these goals, both acute and preventive measures need to be utilized. Acute or abortive therapies are utilized by patients with migraine to stop the attack once begun. This is often problematic in patients with CM as the need for acute treatment—and the risk of MOH—are high. Consequently, building therapeutic strategies for the spectrum of attacks, rather than defining a patient's profile, is important.[23] This is accomplished by providing appropriate drugs and formulations to match the treatment needs of each patient. For almost all patients with CM, preventive therapies are appropriate.[24] Regular follow-up involving review of the patient's headache diary provides an opportunity to refine and optimize treatment efforts. The use and evaluation of preventive care may be guided by headache assessment tools such as the Headache Impact Test[25] or the Migraine Disability Assessment questionnaire.[26]

Selecting abortive treatment

Patients with CM have significant need for abortive medications and are at high risk for MOH. Thus, treatment needs to be patient-specific and the health care provider needs to provide the best therapeutic choice for the specific presentations of migraine that the patient experiences. For example, since an early morning migraine is often associated with nausea, providing an oral medication is unlikely to be effective. Therefore, an injectable or nasal spray is more likely to achieve a better outcome and ultimately, less medication utilization. Gastric stasis or gastric atony is common in migraine patients, resulting in poor absorption of oral medications. Such patients often have an inconsistent response to oral medications. On the other hand, a person with migraine that has a definite mild headache phase will likely respond well to early intervention with a triptan or nonsteroidal anti-inflammatory drug (NSAID). Another factor to consider in selecting treatment is the patient's treatment dynamics. Some patients, for example, "wait to see" if the headache attack will merit use of a prescription medication. Others reserve their prescription medication in case they have a worse headache in the future.

Patients with CM often need more than 1 formulation of abortive medication; a wide variety is available. Migraine-specific medications such as triptans, dihydroergotamine, and ergotamine target 5-$HT_{1B/1D}$ receptors on blood vessels and pain-sensing nerves. 5-$HT_{1B/1D}$ receptor agonists are generally the most effective agents available in aborting the attack and related symptoms.[27] Among the 5-$HT_{1B/1D}$ receptor agonists, sumatriptan is the most effective abortive treatment for migraine.[28,29] Sumatriptan tablets are commonly used, but are less effective than the nasal spray or especially, injectable formulations.[30] Consequently, sumatriptan tablets are more likely to be overused and cause MOH.

Contraindications, adverse events, and cost are important considerations in treatment selection. It is also important to keep in mind that the ineffectively treated migraine has a significant cost associated with it in terms of increased medical utilization, impact at home and in the workplace, and most of all, to the individual.[31]

Non–migraine-specific medications can also be highly effective and should be provided as a therapeutic tool based on their efficacy, rather than on convenience, availability, or cost. Treatment that is most likely to rapidly, safely, and completely abort a migraine attack and provide sustained normal functioning for the patient should be selected. One ineffective approach is to stage acute treatment or arbitrarily begin with 1 medication and add another if the first is ineffective. This approach often does little more than add attack-related disability and increase the likelihood of therapeutic failure. Instead, it is often best to combine acute treatments at the outset based on what is likely to be effective, including nonprescription analgesics, prescription NSAIDs, antiemetics, and triptans.

CASE STUDY (*continued*): Rita's primary care provider diagnosed her with CM and MOH. She was started on amitriptyline to improve sleep, treat depression, and as preventive therapy to reduce migraine frequency. She is instructed to slowly titrate the dose to 75 mg at bedtime. In addition. Rita is provided with specific acute treatment strategies. She is advised to initiate treatment early when the pain is escalating, but still mild to moderate. She was provided with subcutaneous sumatriptan as first-line treatment for migraine associated with nausea and for rescue and advised to not use sumatriptan more than

2 days per week. She is provided with diclofenac potassium to use on alternate days if needed, but also fewer than 2 days per week. Goals are established to improve acute treatment outcome and reduce the overall quantity of acute medications being used. She agrees to return in 2 weeks for a follow-up visit.

Preventive treatment

Preventive therapy is of central importance in the management of patients with CM. Preventive therapy is appropriate in those: (1) who experience ≥2 attacks/month that produce disability that lasts ≥3 days/month; (2) who have a contraindication to or failure of abortive treatments; (3) who use an abortive medication >2 times per week; or (4) with an uncommon migraine condition, such as hemiplegic migraine, migraine with prolonged aura, or migrainous infarction.[32] In addition, preventive therapy should be utilized in those with comorbidities and those with increasing frequency of EM to prevent the transformation into CM.

A wide variety of medications that work as preventive treatment for EM have also been utilized as preventive therapy for CM. However, their efficacy in CM is uncertain, as few have actually been studied in CM. Two medications that have been evaluated specifically as preventatives in patients with CM are topiramate and onabotulinumtoxinA. Only onabotulinumtoxinA has been approved by the US Food and Drug Administration (FDA) for the indication of CM.

Topiramate

The efficacy of topiramate as preventive therapy for CM has been studied in 306 patients with CM.[33] Topiramate 100 mg/day was associated with a 5.8 day reduction in headache days per month compared with 4.7 days for placebo (P=.067). Significant improvements were observed in patient disability and quality of life. For example, 69% of patients treated with topiramate experienced a 25% or greater reduction in the number of headache days per month compared with 52% of placebo-treated patients (P=.005). Reductions were observed with topiramate compared with placebo in worst daily severity of migraine (P = .016), severity of photophobia (P = .032), as well as frequency of vomiting (P = .018), photophobia (P = .038), phonophobia (P = .010), unilateral pain (P = .015), pulsatile pain (P = .023), and pain worsened by physical activity (P = .047).

OnabotulinumtoxinA

Used in conditions such as spasticity for more than 2 decades, onabotulinumtoxinA inhibits the vesicular release of acetylcholine from neurons, resulting in partial chemical denervation of the muscle. In animals and trigeminal cell cultures, onabotulinumtoxinA blocks vesicular release of calcitonin gene-related peptide through the same synaptosomal-associated protein of 25 kDa (SNAP-25) mechanisms occurring in motor neurons.[34,35] Both of these mechanisms may have relevance to the efficacy of onabotulinumtoxinA in migraine.

The efficacy and safety of onabotulinumtoxinA in patients with CM have been investigated in 2 prospective, randomized, multicenter clinical trials: the Phase III Research Evaluating Migraine Prophylaxis Therapy (PREEMPT) trials.[36,37] In both PREEMPT trials, patients were randomized to onabotulinumtoxinA 155 to 195 units or placebo every 12 weeks for 2 cycles. In the PREEMPT 1 trial (N = 679), the mean change in number of headache episodes, the primary efficacy endpoint, was similar for onabotulinumtoxinA and placebo (–5.2 vs –5.3, respectively; P = .344), although the numbers of headache days (P = .006) and migraine days (P = .002) were lower with onabotulinumtoxinA.[36] In the PREEMPT 2 trial (N = 705), the mean change in frequency of headache days per 28 days, the primary efficacy endpoint, was significantly improved with onabotulinumtoxinA compared with placebo (–9.0 vs –6.7, respectively; P < .001).[37] In the subset of patients with CM and MOH, a planned pooled analysis showed greater improvement in number of headache days and all secondary endpoints.[38]

A planned pooled analysis of all patients included in PREEMPT 1 and 2 showed that, with the exception of frequency of acute headache pain medication intake, improvements in all secondary endpoints were significantly greater with onabotulinumtoxinA than placebo.[39] Secondary endpoints included frequency of migraine days, frequency of moderate/severe headache days, number of cumulative hours of headache on headache days, proportion of patients with severe (≥60 points) Headache Impact Test scores, frequency of headache episodes, and frequency of migraine episodes. Most adverse events were mild or moderate in severity and resolved without sequelae. The most frequently reported adverse events leading to discontinuation were neck pain (0.6%), muscular weakness (0.4%), headache (0.4%), and migraine (0.4%) in the onabotulinumtoxinA group.

OnabotulinumtoxinA has been compared with topiramate as preventive therapy in a randomized, double-blind, pilot study involving 59 patients with CM.[40] Following 12 weeks of treatment, significant improvement in the treatment responder rate and all secondary endpoints, including quality of life, was observed in patients treated with either onabotulinumtoxinA or topiramate, with no difference between groups. These efficacy results as preventive therapy are similar to an earlier pilot study in 60 patients treated with onabotulinumtoxinA (maximum 200 units/3 months) or topiramate 100 mg/day over 9 months.[41] Adverse events with onabotulinumtoxinA were generally characterized by weakness in muscle groups in the local vicinity of injection sites around the head and neck (especially eyebrow/eyelid and forehead/neck), while those with topiramate

generally involved systemic effects such as cognitive deficits, paresthesias, loss of appetite, and weight loss. Treatment-related discontinuation occurred in 7.7% of patients treated with onabotulinumtoxinA and 24.1% of patients treated with topiramate.[41]

CASE STUDY (*continued*): Rita returns in 3 months. She is sleeping better and her mood is improved, but she continues with 18 headache days per month. She has reduced her work absenteeism with use of subcutaneous sumatriptan and diclofenac potassium, but continues with significant migraine-related disability at home. Rita and her primary care provider discuss the need for modifying her preventive treatment plan and agree to a trial of at least 2 injection cycles of onabotulinumtoxinA. Rita is reminded of the importance of not overusing her abortive medications and is provided with additional diaries to track her acute treatment successes and failures as well as the number of headache days she experiences.

SUMMARY

Chronic migraine is a frequent, severely disabling headache that often evolves from EM. Treatment should be individualized with consideration of the patient as a whole person rather than just the headaches. Many options have been used for acute and preventive pharmacologic management, although good scientific and clinical evidence is limited to a few options. Evidence supports the efficacy and tolerability of both topiramate and onabotulinumtoxinA for prevention of CM headaches. However, only onabotulinumtoxinA is approved by the FDA for preventive treatment of CM. ●

REFERENCES

1. Stovner L, Hagen K, Jensen R, et al. The global burden of headache: a documentation of headache prevalence and disability worldwide. *Cephalalgia*. 2007;27(3):193-210.
2. Raggi A, Leonardi M, Bussone G, D'Amico D. A 3-month analysis of disability, quality of life, and disease course in patients with migraine. *Headache*. 2013;53(2):297-309.
3. Buse DC, Manack AN, Fanning KM, et al. Chronic migraine prevalence, disability, and sociodemographic factors: results from the American Migraine Prevalence and Prevention Study. *Headache*. 2012;52(10):1456-1470.
4. Serrano D, Manack AN, Reed ML, Buse DC, Varon SF, Lipton RB. Cost and predictors of lost productive time in chronic migraine and episodic migraine: results from the American Migraine Prevalence and Prevention (AMPP) Study. *Value Health*. 2013;16(1):31-38.
5. Walling AD, Woolley DC, Molgaard C, Kallail KJ. Patient satisfaction with migraine management by family physicians. *J Am Board Fam Pract*. 2005;18(6):563-566.
6. Lipton RB, et al. Suboptimal treatment of episodic migraine may mean progression to chronic migraine. *Cephalalgia*. 2013;33(11):954-992. Abstract.
7. Headache Classification Subcommittee of the International Headache Society. The International Classification of Headache Disorders: 2nd edition. *Cephalalgia*. 2004;24(suppl 1):9-160.
8. Silberstein SD, Olesen J, Bousser MG, et al; International Headache Society. The International Classification of Headache Disorders, 2nd Edition (ICHD-II)—revision of criteria for 8.2 Medication-overuse headache [published correction appears in *Cephalalgia*. 2006;26(3):360]. *Cephalalgia*. 2005;25(6):460-465.
9. Petrusic I, Zidverc-Trajkovic J, Podgorac A, Sternic N. Underestimated phenomena: higher cortical dysfunctions during migraine aura. *Cephalalgia*. 2013;33(10):861-867.
10. Cady R, Farmer K, Dexter JK, Schreiber C. Cosensitization of pain and psychiatric comorbidity in chronic daily headache. *Curr Pain Headache Rep*. 2005;9(1):47-52.
11. Headache Classification Committee of the International Headache Society (HIS). The International Classification of Headache Disorders, 3rd edition (beta version). *Cephalalgia*. 2013;33(9):629-808.
12. Katsarava Z, Buse DC, Manack AN, Lipton RB. Defining the differences between episodic migraine and chronic migraine. *Curr Pain Headache Rep*. 2012;16(1):86-92.
13. Lipton RB. Chronic migraine, classification, differential diagnosis, and epidemiology. *Headache*. 2011;51(suppl 2):77-83.
14. Lipton RB, Bigal ME, Diamond M, Freitag F, Reed ML, Stewart WF; AMPP Advisory Group. Migraine prevalence, disease burden, and the need for preventive therapy. *Neurology*. 2007;68(5):343-349.
15. Buse DC, Manack A, Serrano D, Turkel C, Lipton RB. Sociodemographic and comorbidity profiles of chronic migraine and episodic migraine sufferers. *J Neurol Neurosurg Psychiatry*. 2010;81(4):428-432.
16. Bigal ME, Serrano D, Reed M, Lipton RB. Chronic migraine in the population: burden, diagnosis, and satisfaction with treatment. *Neurology*. 2008;71(8):559-566.
17. Stokes M, Becker WJ, Lipton RB, et al. Cost of health care among patients with chronic and episodic migraine in Canada and the USA: results from the International Burden of Migraine Study (IBMS). *Headache*. 2011;51(7):1058-1077.
18. Lipton RB, Bigal ME. Migraine: epidemiology, impact, and risk factors for progression. *Headache*. 2005;45(suppl 1):S3-S13.
19. Ashina S, Lipton RB, Bigal ME. Treatment of comorbidities of chronic daily headache. *Curr Treat Options Neurol*. 2008;10(1):36-43.
20. Kristoffersen ES, Aaseth K, Grande RB, Lundqvist C, Russell MB. Self-reported efficacy of complementary and alternative medicine: the Akershus study of chronic headache. *J Headache Pain*. 2013;14(1):36.
21. Diener HC, Kronfeld K, Boewing G, et al; GERAC Migraine Study Group. Efficacy of acupuncture for the prophylaxis of migraine: a multicentre randomised controlled clinical trial [published correction appers in *Lancet Neurol*. 2008;7(6):475]. *Lancet Neurol*. 2006;5(4):310-316.
22. Linde K, Allais G, Brinkhaus B, Manheimer E, Vickers A, White AR. Acupuncture for migraine prophylaxis. *Cochrane Database Syst Rev*. 2009;(1):CD001218.
23. Diamond M, Cady R. Initiating and optimizing acute therapy for migraine: the role of patient-centered stratified care. *Am J Med*. 2005;118(suppl 1):18S-27S.
24. Lipton RB, Stewart WF, Diamond S, Diamond ML, Reed M. Prevalence and burden of migraine in the United States: data from the American Migraine Study II. *Headache*. 2001;41(7):646-657.
25. Yang M, Rendas-Baum R, Varon SF, Kosinski M. Validation of the Headache Impact Test (HIT-6™) across episodic and chronic migraine. *Cephalalgia*. 2011;31(3):357-367.
26. Stewart WF, Lipton RB, Kolodner KB, Sawyer J, Lee C, Liberman JN. Validity of the Migraine Disability Assessment (MIDAS) score in comparison to a diary-based measure in a population sample of migraine sufferers. *Pain*. 2000;88(1):41-52.
27. Reddy DS. The pathophysiological and pharmacological basis of current drug treatment of migraine headache. *Expert Rev Clin Pharmacol*. 2013;6(3):271-288.
28. Jamieson DG. The safety of triptans in the treatment of patients with migraine. *Am J Med*. 2002;112(2):135-140.
29. Saxena PR, Tfelt-Hansen P. Triptans, 5-$HT_{1B/1D}$ agonists in the acute treatment of migraine. In: Olesen J, Goadsby PJ, Ramadan NM, Tfelt-Hansen P, Welch KMA, eds. *The Headaches*. 3rd ed. Philadelphia, PA: Lippincott Williams & Wilkins; 2006:469-503.
30. Silberstein SD, Marcus DA. Sumatriptan: treatment across the full spectrum of migraine. *Expert Opin Pharmacother*. 2013;14(12):1659-1667.
31. Rapoport AM. Recurrent migraine: cost-effective care. *Neurology*. 1994;44(5 suppl 3):S25-S28.
32. Snow V, Weiss K, Wall EM, Mottur-Pilson C; American Academy of Family Physicians; American College of Physicians-American Society of Internal Medicine. Pharmacologic management of acute attacks of migraine and prevention of migraine headache. *Ann Intern Med*. 2002;137(10):840-849.
33. Silberstein S, Lipton R, Dodick D, et al. Topiramate treatment of chronic migraine: a randomized, placebo-controlled trial of quality of life and other efficacy measures. *Headache*. 2009;49(8):1153-1162.
34. Durham PL. CGRP-receptor antagonists—a fresh approach to migraine therapy? *N Engl J Med*. 2004;350(11):1073-1075.
35. Aoki KR. Evidence for antinociceptive activity of botulinum toxin type A in pain management. *Headache*. 2003;43(suppl 1):S9-15.
36. Aurora SK, Dodick DW, Turkel CC, et al; PREEMPT 1 Chronic Migraine Study Group. OnabotulinumtoxinA for treatment of chronic migraine: results from the double-blind, randomized, placebo-controlled phase of the PREEMPT 1 trial. *Cephalalgia*. 2010;30(7):793-803.
37. Diener HC, Dodick DW, Aurora SK, et al; PREEMPT 2 Chronic Migraine Study Group. OnabotulinumtoxinA for treatment of chronic migraine: results from the double-blind, randomized, placebo-controlled phase of the PREEMPT 2 trial. *Cephalalgia*. 2010;30(7):804-814.
38. Silberstein SD, Blumenfeld AM, Cady RK, et al. OnabotulinumtoxinA for treatment of chronic migraine: PREEMPT 24-week pooled subgroup analysis of patients who had acute headache medication overuse at baseline. *J Neurol Sci*. 2013;331(1-2):48-56.
39. Dodick DW, Turkel CC, DeGryse RE, et al; PREEMPT Chronic Migraine Study Group. OnabotulinumtoxinA for treatment of chronic migraine: pooled results from the double-blind, randomized, placebo-controlled phases of the PREEMPT clinical program. *Headache*. 2010;50(6):921-936.
40. Cady RK, Schreiber CP, Porter JA, Blumenfeld AM, Farmer KU. A multi-center double-blind pilot comparison of onabotulinumtoxinA and topiramate for the prophylactic treatment of chronic migraine. *Headache*. 2011;51(1):21-32.
41. Mathew NT, Jaffri SF. A double-blind comparison of onabotulinumtoxina (BOTOX) and topiramate (TOPAMAX) for the prophylactic treatment of chronic migraine: a pilot study. *Headache*. 2009;49(10):1466-1478.

SUPPLEMENT TO
THE JOURNAL OF
FAMILY
PRACTICE