RELIAS MEDIA

Internal Medicine

Evidence-based summaries of the latest research in internal medicine [ALERT]

Vol. 42, Issue 2, January 30, 2020
ReliasMedia.com

ABSTRACT & COMMENTARY

Menopausal Hormonal Therapy and Breast Cancer Risk: Are Old Data Relevant to Today's Practice?

By Jeffrey T. Jensen, MD, MPH

Leon Speroff Professor and Vice Chair for Research, Department of OB/GYN, Oregon Health & Science University, Portland

Dr. Jensen reports he is a consultant for and receives grant/research support from ObstetRx, Bayer, Merck, and Sebela; he receives grant/research support from AbbVie, Mithra, and Daré Bioscience; and he is a consultant for CooperSurgical and the Population Council.

SYNOPSIS: An individual-participant meta-analysis of prospective studies revealed menopausal hormone therapy associated with an elevation in the risk of breast cancer, with the highest risks associated with daily combined therapy.

SOURCE: Collaborative Group on Hormonal Factors in Breast Cancer. Type and timing of menopausal hormone therapy and breast cancer risk: Individual participant meta-analysis of the worldwide epidemiological evidence. *Lancet* 2019;394:1159-1168.

The Collaborative Group on Hormonal Factors in Breast Cancer, a United Kingdom-based research group, was established in 1992 with the goal of bringing together published and unpublished epidemiologic studies on breast cancer risk associated with the use of menopausal hormonal therapy (MHT).

For this report, the group identified and analyzed anonymized information on individual participants from 58 studies (24 prospective, 34 retrospective) of postmenopausal women. This included 143,887 cases of invasive breast cancer and 424,972 controls without breast cancer published between 1992 and 2018. They categorized MHT use as estrogen-only (ET) or combined estrogen-progestogen (EPT) and evaluated the effect of age at first use, duration of use, time since last use, and preparation last used. Breast cancers were classified as estrogen-receptor positive or negative (ER+ or ER-); ductal or lobular; and localized or spread beyond the breast (e.g., metastatic).

Financial Disclosure: *Internal Medicine Alert's* Physician Editor Stephen Brunton, MD, is a retained consultant for Abbott Diabetes, Acadia, AstraZeneca, and Boehringer Ingelheim; and he serves on the speakers bureau of AstraZeneca, Boehringer Ingelheim, Janssen, Lilly, and Novo Nordisk. Peer Reviewer Gerald Roberts, MD; Editor Jonathan Springston; Editor Jason Schneider; Editorial Group Manager Leslie Coplin; and Accreditations Manager Amy M. Johnson, MSN, RN, CPN, report no financial relationships relevant to this field of study.

Internal Medicine
Evidence-based summaries of the latest research in internal medicine [ALERT]

Internal Medicine Alert (ISSN 0195-315X) is published semimonthly by Relias LLC, 1010 Sync St., Ste. 100, Morrisville, NC 27560-5468. Periodicals postage paid at Morrisville, NC, and additional mailing offices. POSTMASTER: Send address changes to *Internal Medicine Alert*, Relias LLC, 1010 Sync St., Ste. 100, Morrisville, NC 27560-5468.

GST Registration Number: R128870672.

SUBSCRIBER INFORMATION
(800) 688-2421
customerservice@reliasmedia.com
ReliasMedia.com

ACCREDITATION
Relias LLC is accredited by the Accreditation Council for Continuing Medical Education (ACCME) to provide continuing medical education for physicians.

Relias LLC designates this enduring material for a maximum of 2 *AMA PRA Category 1 Credit(s)™*. Physicians should claim only credit commensurate with the extent of their participation in the activity.

This Enduring Material activity, *Internal Medicine Alert*, has been reviewed and is acceptable for credit by the American Academy of Family Physicians. Term of approval begins 1/15/2020. Term of approval is for one year from this date. Physicians should claim only the credit commensurate with the extent of their participation in the activity. Approved for 2 AAFP Prescribed credits.

The American Osteopathic Association has approved this continuing education activity for up to 2 AOA Category 2-B credits.

Successful completion of this CME activity, which includes participation in the evaluation component, enables the participant to earn up to 2 MOC Medical Knowledge points in the American Board of Internal Medicine's (ABIM) Maintenance of Certification (MOC) program. Participants will earn MOC points equivalent to the amount of CME credits claimed for the activity. It is the CME activity provider's responsibility to submit participant completion information to ACCME for the purpose of granting ABIM MOC credit.

This CME activity is intended for the internist/family physician. It is in effect for 36 months from the date of the publication.

The meta-analysis results showed that every MHT type (except vaginal estrogen) increased the risk of breast cancer. The risk estimates increased with longer duration of use and were greater for EPT than ET (years 1-4: EPT relative risk [RR], 1.60; 95% confidence interval [CI], 1.52-1.69), ET RR, 1.17; 95% CI, 1.10-1.26; years 5-14: EPT RR, 2.08; 95% CI, 2.02-2.15; ET RR, 1.33; 95% CI, 1.28-1.37). The risk associated with continuous EPT (RR, 2.3; 95% CI, 2.21-2.40) exceeded that of nondaily progestogen therapy (RR, 1.93; 95% CI, 1.84-2.01). However, the types of estrogens and progestogens, and the routes of administration, did not affect risk further. After ceasing MHT, some excess risk persisted for more than 10 years. Of interest, obesity reduced the overall effect of an excess risk of MHT on breast cancer.

Putting these results together, the Collaborative Group concluded that five years of MHT, starting at age 50 years, would result in one additional breast cancer case in every 50 users of daily EPT, one in every 70 users of nondaily EPT, and one in every 200 users of ET. Continuing the use of MHT for 10 years would double these estimates. They estimated that about 1 million of the approximately 20 million breast cancer cases diagnosed since 1990 in Western countries may have been caused by MHT use.

■ COMMENTARY

The publication of this large individual participant meta-analysis of breast cancer risk with MHT did not generate much news. This is somewhat surprising, considering the inclusion of attributable risk data suggesting that MHT may have directly caused up to one in 20 cases of breast cancer. One explanation could be that in the post Women's Health Initiative (WHI) world, there are fewer users of MHT and less interest by the public and clinicians. We seem more distracted by herbicides and general environmental contamination.

On a more optimistic note, the lack of interest may reflect the consensus that this report provided no new information. Prior research, including many of the publications in the meta-analysis, has documented a small increase in breast cancer risk associated with MHT, and further demonstrates the risk primarily associated with combined EPT. The American Cancer Society lists combined MHT as one of several factors with risk estimates below 2.0 in the most recent Breast Cancer Facts and Figures report. Other factors associated with this level of risk include alcohol use, physical inactivity, and obesity.

To be fair, any increase in risk associated with a modifiable factor may be important; the question is whether this study should influence current practice. All epidemiologic studies require careful assessment of baseline confounding factors that may influence the outcome. In this meta-analysis, the authors adjusted for age, alcohol use, parity, and age at first birth. Commonly, missing data are imputed according to a predefined algorithm. Although well-intentioned, all this affects the accuracy of the final estimate. A meta-analysis cannot correct underlying flaws in the original studies. In contrast, meta-analyses frequently magnify these errors by creating tight confidence intervals around risk estimates that exaggerate significance. Risk estimates less than 2.0 are considered weak effects, and should be viewed with extreme caution unless obtained under the rigorous conditions of a well-designed, double-blind, randomized trial.

For this reason, the WHI still provides the best estimates of risk from MHT. In WHI, the use of combined daily EPT resulted in a significantly elevated hazard ratio (HR) for breast cancer (HR, 1.24; 95% CI, 1.01-1.54).[1] However, the magnitude of the increase is small, and statistical significance was lost in most subanalyses. Perhaps of greater interest is the reduction in breast cancer risk observed in the WHI ET arm. Anderson et al found that the use of estrogen only for a median of 5.9 years was associated with a significantly lower incidence of invasive breast cancer compared with placebo (HR, 0.77; 95% CI, 0.62-0.95), with no significant difference in risk reduction in those women diagnosed during the intervention phase (21% decrease) and post-intervention (25% decrease).[2] Even more impressively, fewer ET-treated women died from breast cancer (HR, 0.37; 95% CI, 0.13-0.91) or from any cause. What I find most impressive in evaluating the WHI results is that the magnitude of the effect of protection with estrogen-only therapy (~60%) is larger than the magnitude of widely quoted increased risk with combined estrogen-progestin therapy (~25%). The

meta-analysis results also reflect practice patterns from many years ago that may no longer be relevant.

After WHI, most clinicians have moved away from combined daily MHT regimens that administer conjugated equine estrogens and medroxyprogesterone acetate. The use of transdermal or vaginal estradiol in physiologic doses prevents adverse effects on cardiovascular outcomes.[3,4] Administration of lower doses of oral natural progesterone or use of the lowest dose levonorgestrel intrauterine systems for endometrial protection may reduce the risk of breast cancer in women using combined therapy. However, it will be years before these data become available. ■

REFERENCES

1. Chlebowski RT, Hendrix SL, Langer RD, et al. Influence of estrogen plus progestin on breast cancer and mammography in healthy postmenopausal women: The Women's Health Initiative Randomized Trial. *JAMA* 2003;289:3243-3253.
2. Anderson GL, Chlebowski RT, Aragaki AK, et al. Conjugated equine oestrogen and breast cancer incidence and mortality in postmenopausal women with hysterectomy: Extended follow-up of the Women's Health Initiative randomised placebo-controlled trial. *Lancet Oncol* 2012;13:476-486.
3. Laliberté F, Dea K, Duh MS, et al. Does the route of administration for estrogen hormone therapy impact the risk of venous thromboembolism? Estradiol transdermal system versus oral estrogen-only hormone therapy. *Menopause* 2018;25:1297-1305.
4. Canonico M, Oger E, Plu-Bureau G, et al. Hormone therapy and venous thromboembolism among postmenopausal women: Impact of the route of estrogen administration and progestogens: The ESTHER study. *Circulation* 2007;115:840-845.

ABSTRACT & COMMENTARY

Dapagliflozin Treatment Improves Life Quality for Systolic Heart Failure Patients

By Jamie L.W. Kennedy, MD, FACC

Associate Professor, Division of Cardiology, Advanced Heart Failure & Transplant Cardiology, University of California, San Francisco

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

SYNOPSIS: Treatment with dapagliflozin for 12 weeks resulted in improved health status, either a reduction in NT-proBNP or improvement in quality of life measures, in systolic heart failure patients with or without type 2 diabetes mellitus.

SOURCE: Nassif ME, Windsor SL, Tang F, et al. Dapagliflozin effects on biomarkers, symptoms and functional status in patients with heart failure with reduced ejection fraction, the DEFINE-HF trial. *Circulation* 2019;140:1463-1476.

Sodium-glucose cotransporter-2 (SGLT2) inhibitors increase urinary excretion of glucose, thereby lowering blood sugar. Several large clinical trials of SGLT2 inhibitors in diabetic patients have shown reductions in heart failure hospitalizations. However, these trials were limited by low numbers of patients with heart failure and lack of details on their cardiac disease, such as prevalence of systolic dysfunction. Of course, heart failure remains a highly morbid and mortal disease despite currently available evidence-based interventions such as medications and devices.

Nassif et al studied the use of one SGLT2 inhibitor, dapagliflozin, in patients with established symptomatic systolic heart failure, defined as ejection fraction ≤ 40% with New York Heart Association (NYHA) class II to III symptoms. Patients with and without type 2 diabetes mellitus were enrolled. Type 1 diabetes patients were excluded, as were patients with recent heart failure hospitalizations and chronic kidney disease stage 4 or 5. Patients were randomized to dapagliflozin or placebo for 12 weeks. The two primary endpoints were a little complex. The first endpoint was the average of six- and 12-week mean NT-proBNP. The second endpoint was a composite of the proportion of patients who achieved a meaningful improvement in health status, defined as either a five-point increase in Kansas City Cardiomyopathy Questionnaire (KCCQ) or a 20% decrease in the average of six- and 12-week NT-proBNP. There were a range of prespecified subgroups and secondary endpoints, too, including heart failure events as an exploratory endpoint.

The 263 patients enrolled in the trial were typical of heart failure studies: 73% male, with average age 61 years; 40% were African-American. Sixty-two percent of patients had type 2 diabetes mellitus, 40% had atrial fibrillation, and 53% had ischemic cardiomyopathy. Two-thirds of patients exhibited NYHA class II symptoms, one-third class III. They were a well-managed group: 97% prescribed beta-blockers, 92% angiotensin-converting enzyme inhibitors/angiotensin II receptor blockers/angiotensin receptor-neprilysin inhibitors (ACE/ARB/ARNI), and 61% aldosterone antagonist. Sixty-two percent presented

with implantable cardioverter-defibrillators, and 35% presented with cardiac resynchronization therapy devices. The average left ventricular ejection fraction was 26%, and the median NT-proBNP on enrollment was 1,136 pg/mL.

The authors did not observe any difference between the groups in the first primary endpoint, the average six- and 12-week mean NT-proBNP (1,133 pg/mL vs. 1,191 pg/mL; $P = 0.43$). However, the second primary endpoint revealed a significant improvement in health status in 61.5% of patients in the treatment arm vs. 50.4% in the control arm ($P = 0.039$). Both components of this composite endpoint favored dapagliflozin: 42.9% vs. 32.5% of patients with a five- or more point increase in KCCQ and 44.0% vs. 29.4% with 20% or more reduction in NT-proBNP.

Overall, safety events were similar between groups, although there were more episodes of volume depletion in the dapagliflozin arm (12 events vs. seven events). Interestingly, there were no differences in the rates of severe hypoglycemia (one patient in each arm, both of whom were diabetics). There was no difference in response rate for diabetics vs. nondiabetics. The authors concluded that treatment with dapagliflozin for 12 weeks resulted in improved health status in systolic heart failure patients with or without type 2 diabetes mellitus.

■ COMMENTARY

The DEFINE-HF study was published contemporaneously with DAPA-HF, a larger study of similar population, which showed treatment with dapagliflozin reduced rates of worsening heart failure or cardiovascular death from 21.2% to 16.3% over a median period of 18.2 months of treatment ($P < 0.001$).[1] Components of the endpoint both favored dapagliflozin as well: cardiovascular death 9.6% vs. 11.5% and worsening heart failure in 10.0% vs. 13.7%.

The mechanisms by which dapagliflozin and other SGLT2 inhibitors benefit patients with heart failure are unclear. Certainly, improved blood sugar control in diabetic patients may limit cardiovascular morbidity and mortality, and urinary excretion of glucose may result in improved control of volume status. Studies also have shown SGLT2 inhibitors lead to a reduction in left ventricular mass in patients with coronary disease and diabetes, alterations in cardiomyocyte metabolism favoring ketone bodies, and reductions in intracellular sodium and calcium.

DEFINE-HF's interesting twist was its focus on quality of life. Physicians and patients always have considered quality of life when making treatment decisions, although the database to guide these discussions has, at times, been thin. However, more recently, tools to assess quality of life, such as the KCCQ, have become available and implemented in clinical trials alongside "hard" endpoints such as mortality and hospitalization. In this particular case, the quality of life data aid the patient and physician in deciding whether to add yet another medication to already-extensive regimens. Most patients in this study were taking at least six medications on enrollment: ACE/ARB/ARNI, beta-blocker, aldosterone antagonist, loop diuretic, lipid-lowering agent, and one or more medications for diabetes. The cost and complexity of these regimens certainly weigh on patients' minds and wallets. Talking with patients about mortality absolute risk reductions in the 2% range, as seen in DAPA-HF, may not be sufficient for some patients to add an additional medication, while a clinically significant improvement in quality of life may be more meaningful.

As we have seen in previous trials, the use of evidence-based heart failure therapies far exceeded that in clinical practice. The benefit of dapagliflozin may be more marked in patients unable to tolerate other evidence-based heart failure medications. Where on the pathway from normal glucose metabolism to insulin dependence were the nondiabetics in this study? The average age and high incidence of coronary disease and dyslipidemia leads me to suspect a sizable number of nondiabetics presented with impaired glucose tolerance, which may explain some of the benefit of dapagliflozin. For example, I am less certain a benefit would be seen in lean young adults with familial cardiomyopathy. I am interested to see if SGLT2 inhibitors are helpful for patients with heart failure with preserved ejection fraction, considering the lack of evidence-based treatment options demonstrating a benefit.

How will these data alter my management of systolic heart failure patients? For patients with type 2 diabetes mellitus and heart failure, dapagliflozin certainly should be part of their medication regimen, perhaps replacing less beneficial medications like sulfonylureas. For nondiabetic patients similar to the populations studied in DEFINE-HF and DAPA-HF, we will discuss dapagliflozin as an additional therapy beyond ACE/ARB/ARNI, beta-blockers, and aldosterone antagonists. For patients significantly different from the populations studied, such as lean young adults with familial cardiomyopathy, I would like to see additional data before routinely prescribing dapagliflozin. Finally, a practical point: Coordination of care with primary care physicians and endocrinologists will be even more important in the future, as we coordinate who prescribes and monitors which medication for which patient. ■

REFERENCE
1. McMurray JJV, Solomon SD, Inzucchi SE, et al. Dapagliflozin in patients with heart failure and reduced ejection fraction. *N Engl J Med* 2019; Sep 19. doi: 10.1056/NEJMoa1911303. [Epub ahead of print].

BRIEF REPORT

What Is the Optimal Blood Pressure for Secondary Prevention of Stroke?

By Matthew E. Fink, MD

Louis and Gertrude Feil Professor and Chair, Department of Neurology, Associate Dean for Clinical Affairs, NYP/Weill Cornell Medical College

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

SOURCE: Kitagawa K, Yamamoto Y, Arima H, et. al, for the Recurrent Stroke Prevention Clinical Outcome (RESPECT) Study Group. Effect of standard vs intensive blood pressure control on the risk of recurrent stroke: A randomized clinical trial and meta-analysis. *JAMA Neurol* 2019;76:1309-1318.

High blood pressure is the most prevalent and important risk factor for stroke. Great efforts have been made to reduce blood pressure (BP) for both primary and secondary stroke prevention. In clinical trials of primary prevention of all cardiovascular events, which includes stroke, lower BP seems to be better in all patients. A systolic BP of < 115 mmHg has been recommended as a target. However, after a stroke, there continues to be controversy and debate over the ideal target BP.

Kitagawa et al randomized 1,280 patients who already had suffered an ischemic or hemorrhagic stroke into two BP treatment arms — standard therapy, defined as BP control with a target lower than 140/90 mmHg, and an intensive treatment arm, with a target lower than 120/80 mmHg. The primary outcome measure was stroke recurrence.

This study was performed in Japan, and it ended early. Of the 1,263 enrolled patients, the mean age was 67.2 years, and 69.4% were male. Almost all patients (99.5%) completed a mean follow-up of 3.9 years, with a mean blood pressure at baseline that was 145.4/83.6 mmHg. In the standard group, throughout overall follow-up, mean BP was 133.2/77.7 mmHg. In the intensive treatment group, the mean BP was 126.7/77.4 mmHg. When comparing the rate of recurrent stroke between the two groups, there was a nonsignificant rate reduction in the intensive group compared to the standard group.

The investigators then pooled their data with findings from three previous randomized, controlled trials in a meta-analysis, and stated that with this larger group, the risk ratio favored intensive BP control (relative risk, 0.78; $P = 0.02$). The authors concluded intensive BP-lowering tended to reduce stroke recurrence and recommended a target BP that is < 130/80 mmHg for secondary stroke prevention.

However, there are problems with the recommendation from Kitagawa et al. They excluded patients 85 years of age and older, and this was a large cohort of stroke patients. The authors showed a significant difference only after conducting a meta-analysis and pooling data from other studies. This was not part of their initial research plan. They terminated the study early before any firm conclusions could be drawn. At this time, we do not have evidence to support a firm recommendation for optimal BP management for secondary stroke prevention. ■

BRIEF REPORT

Stable Coronary Disease and Atrial Fibrillation Patients Best Treated With Rivaroxaban Alone

By Matthew E. Fink, MD

Louis and Gertrude Feil Professor and Chair, Department of Neurology, Associate Dean for Clinical Affairs, NYP/Weill Cornell Medical College

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

SOURCE: Yasuda S, Kaikita K, Akao M, et al. Antithrombotic therapy for atrial fibrillation with stable coronary disease. *N Engl J Med* 2019;381:1103-1113.

Optimal antithrombotic therapy for stroke prevention in patients with atrial fibrillation continues to evolve. Subcategories may require different types of therapy.

This Japanese study was performed as a multicenter, open-label trial. The authors enrolled 2,236 patients with atrial fibrillation who underwent percutaneous coronary intervention or bypass grafting more than a year earlier and who were stable. Subjects were randomized to receive monotherapy with rivaroxaban alone or combination therapy with rivaroxaban plus a single antiplatelet agent. The primary endpoint was a composite of stroke, systemic embolism, myocardial infarction, unstable angina, or death from any cause, and it was analyzed for noninferiority. The primary safety endpoint was major bleeding. This trial ended early because of increased mortality in the combination therapy group of rivaroxaban plus an antiplatelet agent. Monotherapy with rivaroxaban was noninferior to combination therapy for the primary efficacy endpoint, with event rates of 4.14% and 5.75% per patient year, respectively.

Regarding the safety endpoint, rivaroxaban was superior, with event rates of 1.62% and 2.76% per patient year, respectively, for a hazard ratio of 0.59 ($P = 0.01$). Because this study was performed only in Japan, caution should be taken before generalizing these findings to other countries with different ethnicities. ■

PHARMACOLOGY UPDATE

Lemborexant Tablets (Dayvigo)

By William Elliott, MD, FACP, and James Chan, PharmD, PhD

Dr. Elliott is Assistant Clinical Professor of Medicine, University of California, San Francisco.
Dr. Chan is Associate Clinical Professor, School of Pharmacy, University of California, San Francisco.

Drs. Elliott and Chan report no financial relationships relevant to this field of study.

The FDA has approved a second dual orexin receptor antagonist (DORA), following suvorexant (2014), to treat insomnia. The orexin signaling pathway plays a role in wakefulness.[1] In individuals with sleep-wake disorders, it is possible that orexin signaling is not functioning normally. Lemborexant will be distributed as Dayvigo, pending scheduling by the Drug Enforcement Administration.

INDICATIONS

Lemborexant should be prescribed to treat adults with insomnia characterized by difficulties with sleep onset and/or sleep maintenance.[1]

DOSAGE

The recommended dose is 5 mg taken immediately before going to bed, with at least seven hours remaining before planned time of awakening.[1] Lemborexant should not be taken more than one time per night. The maximum dose of lemborexant is 10 mg. In patients with moderate hepatic impairment, the dose is 5 mg.

Food delays the peak plasma concentration of lemborexant; taking the drug after a meal may delay the time to sleep onset. Lemborexant is available as a 5 mg tablet and as a 10 mg tablet.

POTENTIAL ADVANTAGES

Lemborexant does not appear to be associated with rebound insomnia or withdrawal effects.[1] Additionally, there are no clinically meaningful effects on driving performance nine hours following a dose (2.5 mg, 5 mg, 10 mg).[2]

POTENTIAL DISADVANTAGES

Central nervous system depression, sleep paralysis, worsening of depression, suicidal ideation, and complex sleep behavior (e.g., sleep walking, sleep driving) may occur with lemborexant.[1] Avoid the concomitant use of lemborexant with strong or moderate CYP3A inhibitors and inducers.[1] The most frequently reported adverse reactions (vs. placebo) were somnolence or fatigue (6.9-9.6% vs. 1.3%) and headache (4.5-5.9% vs. 3.4%).[1] At doses between 10 mg and 30 mg, lemborexant showed abuse potential similar to zolpidem 30 mg and suvorexant 40 mg.[1]

COMMENTS

The approval of lemborexant was based on the results from two Phase III studies that included subjects with insomnia disorder characterized by difficulties with sleep onset and/or sleep maintenance.[1] Study 1 was a six-month investigation of adult subjects randomized to lemborexant 5 mg (n = 325), 10 mg (n = 323), or placebo (n = 325). The primary outcome was subject-reported sleep onset latency (sSOL), defined as the time from attempt to sleep until sleep onset. Sleep maintenance was a secondary endpoint, assessed by sleep efficiency and wake after sleep onset (WASO).

At six months, both doses of lemborexant reduced sleep onset by 30% (baseline of 43 minutes and 45 minutes to 20 minutes and 19.2 minutes, respectively, vs. 45 minutes to 27.3 minutes for placebo). The percent of time asleep while in bed improved, and the time awake after sleep onset shortened.

Study 2 was a one-month randomized, double-blind, placebo- and active-controlled investigation of older adults (women ≥ age 55 years, men ≥ age 65 years). Subjects were randomized to lemborexant 5 mg (n = 266), 10 mg (n = 269), placebo (n = 208), or 6.25 mg of zolpidem (n = 263).[1,3] The primary endpoint was latency to persistent sleep at days 29-30 as measured by overnight polysomnography (PSG) monitoring. Secondary endpoints were sleep efficiency and WASO.

Sleep onset improved by 20% and 30% with the 5 mg and 10 mg doses, respectively, compared to placebo (mean reduction of 17-20 minutes vs. seven reduction minutes for placebo). Sleep efficiency and WASO also improved significantly. Both doses of lemborexant were much more effective than zolpidem, based on PSG data, but only more effective on sleep sSOL based on self-reported data. Dosing of lemborexant at night resulted in impairment of balance at four hours compared to placebo, but no difference was detected in ability to awaken to sound.[1] The dose range of 2.5-10 mg proved efficacious and still minimized next-morning residual sleepiness.[4]

CLINICAL IMPLICATIONS

Insomnia is a prevalent disorder, with short-term insomnia affecting 30-50% of the population, and chronic insomnia affecting 5-10%.[5] FDA-approved drugs include benzodiazepines (temazepam, triazolam), nonbenzodiazepine Z-drugs (eszopiclone, zaleplon, zolpidem), DORA (suvorexant, lemborexant), melatonin receptor agonists (ramelteon), antidepressants (doxepin), and others used off-label (e.g., diphenhydramine, trazodone).

Suvorexant is better for sleep maintenance than for reducing sleep latency. In fact, the American Academy of Sleep Medicine (AASM) does not recommend suvorexant for reducing sleep latency.[5,6]

Lemborexant appears to be effective in reducing sleep latency and improving sleep maintenance, but has not demonstrated clear advantages over existing drugs. AASM recommends considering suvorexant or doxepin for sleep maintenance; eszopiclone, temazepam, and zolpidem ER for sleep onset and sleep maintenance; and zaleplon, triazolam, ramelteon, or zolpidem IR for sleep onset insomnia. The FDA has recommended classifying lemborexant as a controlled substance. A decision on scheduling is expected by February. Price is not available yet. ■

REFERENCES

1. Eisai Inc. Dayvigo Prescribing Information, December 2019. Available at: http://bit.ly/36HMcBw. Accessed Jan. 10, 2020.
2. Vermeeren A, Jongen S, Murphy P, et al. On-the-road driving performance the morning after bedtime administration of lemborexant in healthy adult and elderly volunteers. *Sleep* 2019; Apr 1;42(4). pii: zsy260. doi: 10.1093/sleep/zsy260.
3. Rosenberg R, Murphy P, Zammit G, et al. Comparison of lemborexant with placebo and zolpidem tartrate extended release for the treatment of older adults with insomnia disorder: A phase 3 randomized clinical trial. *JAMA Netw Open* 2019;2:e1918254.
4. Murphy P, Moline M, Mayleben D, et al. Lemborexant, a dual orexin receptor antagonist (DORA) for the treatment of insomnia disorder: Results from a Bayesian, adaptive, randomized, double-blind, placebo-controlled study. *J Clin Sleep Med* 2017;13:1289-1299.
5. Sateia MJ, Buysse DJ, Krystal AD, et al. Clinical practice guideline for the pharmacologic treatment of chronic insomnia in adults: An American Academy of Sleep Medicine clinical practice guideline. *J Clin Sleep Med* 2017;13:307-349.
6. Abad VC, Guilleminault C. Insomnia in elderly patients: Recommendations for pharmacological management. *Drugs Aging* 2018;35:791-817.

CME INSTRUCTIONS

To earn credit for this activity, please follow these instructions:
1. Read and study the activity, using the provided references for further research.
2. Log on to **ReliasMedia.com** and click on My Account. First-time users must register on the site. Tests are taken after each issue.
3. Pass the online test with a score of 100%; you will be allowed to answer the questions as many times as needed to achieve a score of 100%.
4. After successfully completing the test, your browser will be automatically directed to the activity evaluation form, which you will submit online.
5. Once the completed evaluation is received, a credit letter will be emailed to you.

CME QUESTIONS

1. Which was a conclusion from the Collaborative Group on Hormonal Factors in Breast Cancer study?
a. Women using combined daily estrogen-progestogen therapy led to an increase in breast cancer risk relative to those using intermittent (nondaily) progestogens.
b. Women using estrogen-only therapy were at a higher risk for breast cancer relative to those using intermittent (nondaily) progestogens.
c. A longer duration of use lowered the risk of breast cancer associated with both estrogen-only and estrogen-progestogen therapy.
d. Five years of menopausal hormonal therapy, starting at age 50 years, would result in five additional breast cancer cases in every 50 users of daily estrogen-progestogen therapy.

2. A study of dapagliflozin in systolic heart failure patients for 12 weeks showed:
a. lower NT-proBNP levels.
b. improved quality of life scores.
c. more hypoglycemia.
d. more hypovolemia.

3. In patients with chronic atrial fibrillation and stable coronary artery disease, the best antithrombotic regimen includes a direct oral-acting anticoagulant and an antiplatelet medication.
a. True
b. False

4. The optimal blood pressure target for secondary stroke prevention is a systolic blood pressure of 140 mmHg.
a. True
b. False

CME OBJECTIVES

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

- describe new findings in the differential diagnosis and treatment of various diseases;
- describe the advantages, disadvantages, and controversies surrounding the latest advances in the diagnosis and treatment of disease;
- identify cost-effective treatment regimens;
- explain the advantages and disadvantages of new disease screening procedures.