

EDITORIAL

Algorithm and mobile app for menopausal symptom management and hormonal/non-hormonal therapy decision making: a clinical decision-support tool from The North American Menopause Society

OVERVIEW

The Menopause Decision-Support Algorithm (Fig. 1) and companion iPhone/iPad app, developed in collaboration with The North American Menopause Society (NAMS), are designed to help clinicians decide which patients are candidates for pharmacologic treatment of menopausal symptoms, understand what the treatment options are, and gain experience deciding among the options. Menopausal symptoms vary dramatically among women.^{1,2} Some women are good candidates for hormonal treatments and others, due to their personal preferences or risk factor profiles, are not appropriate candidates and should consider non-hormonal options. One of the most complex health care decisions facing women in mid-life is whether to use prescription medications for menopausal symptom management, and the array of pharmacologic options has expanded markedly in recent years.^{2,3} This new app, which can be downloaded free of charge on a mobile phone or tablet device, helps clinicians and patients work together to “personalize” treatment decisions, based on risk stratification⁴⁻⁹ and the patient’s personal preferences. The mobile app has two modes, one for clinicians and a companion mode for patients, to facilitate shared decision making and patient-centered care.

The algorithm and mobile app address options for “moderate to severe” hot flashes and/or night sweats (defined as bothersome enough to interfere with daily activities, impair quality of life, and/or interrupt sleep), as well as genitourinary symptoms (including vaginal dryness or pain with intercourse or other sexual activities). Convenient links provide information about treatment options, formulations and doses, and contraindications to therapy. The app calculates an atherosclerotic cardiovascular disease (CVD) risk score for each patient,¹⁰ which is relevant to the decision regarding initiation of systemic menopausal hormone therapy (HT). Women at high risk of, or with significant concern about, breast cancer should be informed about availability of non hormonal therapies. Once the clinician becomes familiar with the algorithm, personalized decision-making for most patients will require only 2-3 minutes, and the app provides a summary at the end that can be printed out or directly emailed to the patient. **The tool can be used for women with menopausal symptoms who are ages ≥45 years old.** The algorithm can also be used for women who have had removal of both ovaries, regardless of age.

Women below age 45 or those who are not clearly menopausal, as well as women who have had endometrial ablation, progestin-releasing intrauterine device/system, or hysterectomy without removal of ovaries, may need additional clinical evaluation before applying this algorithm (evaluation may include hCG, FSH, TSH, prolactin, and other tests).³ The algorithm encourages all patients to try lifestyle modifications for at least 3 months before beginning HT or other pharmacologic therapies. For information on lifestyle modifications, cognitive behavioral therapy, and/or alternative remedies, clinicians may want to print out the materials for the patient at the below link (or send the link by email via the app): <http://www.menopause.org/docs/for-women/mnflashes.pdf>. Women at high risk of osteoporotic fracture and unable to tolerate standard preventive medications may also be candidates for HT (NAMS Hormone Therapy Position Statement: <http://www.menopause.org/docs/default-document-library/psht12.pdf?sfvrsn=2>).² The algorithm also addresses considerations relevant to decisions about duration of treatment, including balancing risks of breast cancer, cardiovascular disease, and osteoporosis.¹⁻³ Each step of the algorithm should be reassessed at least once every 12 months or if health status changes.

BACKGROUND

Women have an increasing number of options, both hormonal and non-hormonal, for the management of menopausal symptoms.¹⁻³ A major deterrent to treatment, however, is the complexity of the decision-making process and the lack of information about available options. This new algorithm and mobile app for menopausal symptom management incorporate state-of-the-science evidence and research to clarify and streamline the decision-making process for both patients and clinicians.

Menopausal HT continues to have an important clinical role in the management of vasomotor and other menopausal symptoms, but it has complex biological effects. The rational use of HT requires balancing the potential benefits and risks of treatment. Although findings from the Women’s Health Initiative (WHI) and other randomized clinical trials have helped to clarify the benefits and risks of HT and provided insights to improve decision making,⁴⁻⁷ current options include lower doses and transdermal formulations that may further minimize risks. Available research suggests that risk stratification based on clinical characteristics of the patient has utility in identifying those for whom benefits of HT are likely to outweigh the

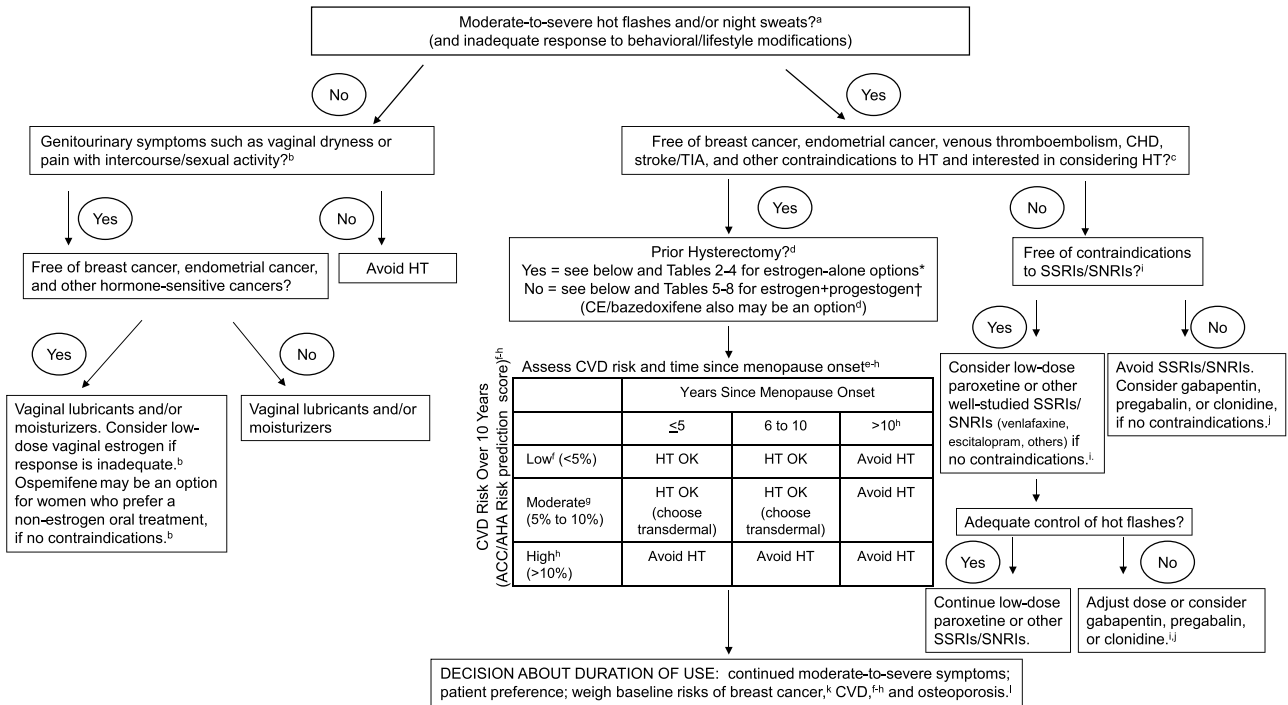


FIG. 1. Algorithm for menopausal symptom management and hormonal/non-hormonal therapy decision making. Algorithm footnotes appear at the end of the article.

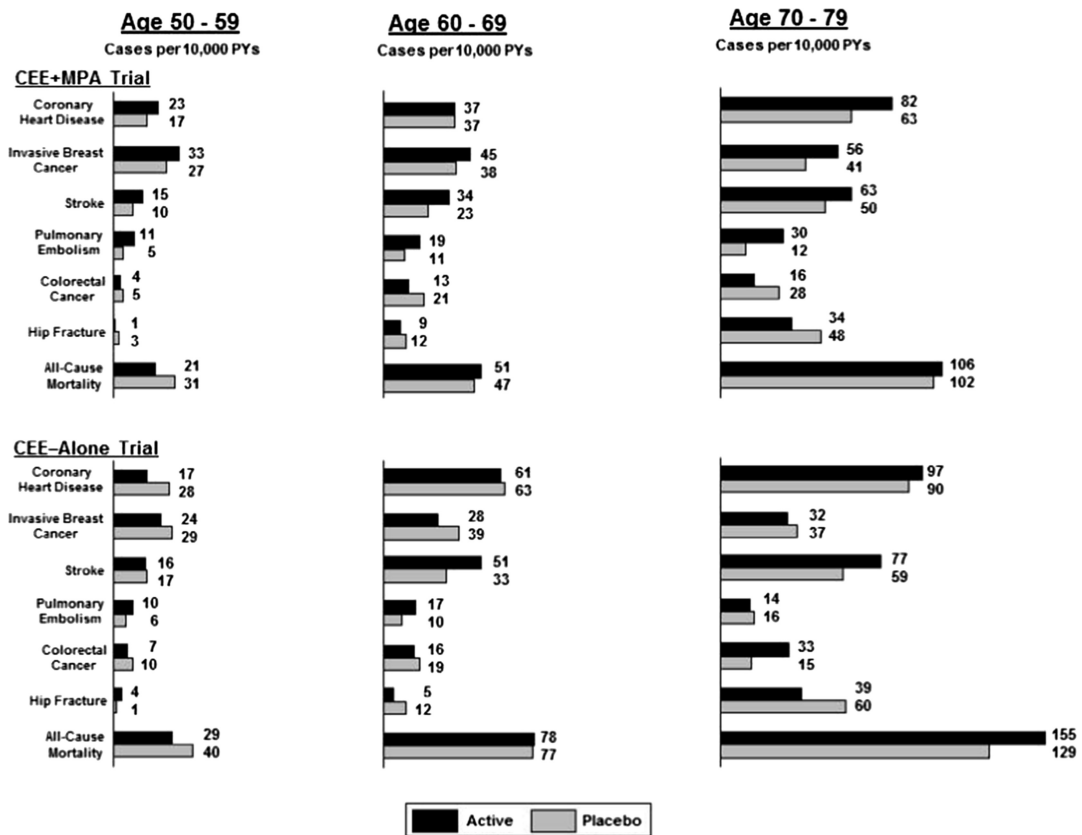


FIG. 2. WHI hormone therapy trials: absolute risks (cases per 10,000 person-years) for outcomes in the intervention phases of the estrogen-progestin and estrogen-alone trials, by age group. Data are from reference 4.

risks.⁴⁻⁹ Age and time since menopause are strong predictors of health outcomes on HT, and the absolute risks of adverse events are much lower in younger than older women (see Fig. 2).⁴ Differences by age have been particularly apparent for estrogen alone among women with hysterectomy.^{4,5} In addition, women at higher baseline cardiovascular risk, due to dyslipidemia, metabolic syndrome, or other cardiometabolic risk factors, have greater risk of adverse vascular outcomes on HT than women at lower risk.²⁻⁷ These findings, based on proximity to menopause, underlying cardiovascular risk, and other personal risk factors, have been incorporated into the decision-making process used in this algorithm. Women who are not candidates for, or do not choose to take, HT can be evaluated for non-hormonal treatments. The use of risk stratification and personalized risk assessment offers promise for improved safety and a more favorable benefit:risk profile for both hormonal and non-hormonal treatments.

DECISION-MAKING PROCESS AND TREATMENT OPTIONS

The key elements of the algorithm (Fig. 1) include assessment of whether the patient has moderate to severe vasomotor symptoms (the primary indication for initiating systemic HT); eliciting the patient's personal preference regarding treatment; evaluating the patient for the presence of any contraindications to systemic HT, as well as the patient's time since menopause onset and baseline risks of CVD and breast cancer; reviewing the benefits and risks of treatment with the patient (giving more emphasis to absolute than to relative measures of effect) (Fig. 2); and, if HT is initiated, regularly reviewing the patient's need for continued treatment. If hormonal treatment is chosen, lower doses may be effective for many women, and the transdermal route may be preferable to oral for patients with metabolic syndrome or other significant CVD risk factors. In appropriate patients, a tissue-selective estrogen complex, such as conjugated estrogens combined with bazedoxifene (a selective estrogen receptor modulator) may be an option. A similar process is followed for non-hormonal treatments in women who are not candidates for, or who choose not to take, hormonal therapy. Paroxetine 7.5 mg/d is an FDA-approved non-hormonal medication for vasomotor symptoms; a wide range of other selective serotonin reuptake inhibitors or serotonin/norepinephrine reuptake inhibitors, as well as gabapentin, pregabalin, and clonidine, can be considered. For patients who do not have moderate or severe hot flashes but have significant genitourinary symptoms (vaginal dryness or pain with intercourse/sexual activities) without adequate response to vaginal lubricants and/or moisturizers, low-dose vaginal estrogen is an option. Ospemifene can also be considered for women without contraindications and who prefer a non-estrogen oral treatment. Clinicians should check product labeling for a comprehensive listing of contraindications and cautions for any medications prescribed.

Whether or not to initiate systemic HT to prevent osteoporosis is controversial, but if done, current guidelines from

NAMS recommend that treatment be limited to women at high risk of osteoporotic fracture who cannot tolerate alternate osteoporosis therapies.²

CONCLUSIONS

Risk stratification can be used to identify appropriate candidates for pharmacologic treatment of menopausal symptoms and to facilitate a safer and more personalized approach to clinical decision making. Recent research has advanced our understanding of the benefits and risks of available treatment options and enhanced the ability of both clinicians and patients to make informed choices about treatment.

Footnotes to Algorithm and Supplemental Tables:

Abbreviations:

HT = menopausal hormone therapy; FDA= Food and Drug Administration; NAMS=North American Menopause Society; CHD=coronary heart disease; TIA=transient ischemic attack; ASCVD= atherosclerotic cardiovascular disease; CVD=cardiovascular disease; ACC/AHA= American College of Cardiology/American Heart Association; ET=estrogen therapy; EPT=estrogen+progestogen therapy; CE=conjugated estrogens; SSRI=selective serotonin reuptake inhibitors; SNRI= serotonin/norepinephrine reuptake inhibitors; hCG=human chorionic gonadotropin; FSH=follicle stimulating hormone; TSH=thyroid stimulating hormone; PRL=prolactin.

^aThis algorithm applies to women with menopausal symptoms who are ≥ 45 years of age. It can also be used for women who have had removal of both ovaries, regardless of age. Women below age 45 or those with uncertain menopausal status may need additional clinical evaluation before applying this algorithm (evaluation may include hCG, FSH, TSH, prolactin, and other tests).³ "Moderate-to-severe hot flashes and/or night sweats" refer to bothersome symptoms that interfere with daily activities, impair quality of life, and/or interrupt sleep. Patients should try lifestyle modifications for at least 3 months before using this algorithm (TAP HERE to see or print out lifestyle modification guidelines for the patient [or send the link by email via the app]: <http://www.menopause.org/docs/for-women/mnflashes.pdf>). For any medications prescribed, clinicians should check product labeling for a comprehensive listing of contraindications and cautions.

Women at high risk of osteoporotic fracture but unable to tolerate standard preventive medications also may be reasonable candidates for systemic HT even if they do not have moderate to severe vasomotor symptoms (TAP HERE to see the NAMS HT Position Statement: <http://www.menopause.org/docs/default-document-library/psht12.pdf?sfvrsn=2>).

^bWomen who have vaginal dryness alone, without moderate to severe vasomotor symptoms, may be candidates for low-dose vaginal estrogen or other treatments. TAP HERE to see Table 1 for vaginal estrogen options. Contraindications for vaginal estrogen include unexplained vaginal bleeding and known or suspected breast cancer or other estrogen-dependent neoplasia. Ospemifene may be an option for women who

prefer a non-estrogen oral treatment. Contraindications for ospemifene include all of those for vaginal estrogen (above), as well as past or current venous or arterial thromboembolic disease. TAP HERE to see other contraindications and cautions. Women should be evaluated on an ongoing basis for genitourinary symptoms, irrespective of other treatments.

^cIs the patient interested in considering HT and free of the following contraindications? TAP HERE to see contraindications/cautions: unexplained vaginal bleeding; liver dysfunction or disease; active or history of deep venous thrombosis or pulmonary embolism; known blood clotting disorder or thrombophilia; untreated hypertension; history of breast, endometrial cancer, or other estrogen-dependent tumor; known hypersensitivity to HT, or history of CHD, stroke, or TIA. Women with one or more 1st degree relatives with breast cancer (BC) or otherwise at increased risk of BC (see Breast Cancer Risk Score at <http://www.cancer.gov/bcrisktool/>) may want to consider non-hormonal therapy. For other contraindications, including high triglycerides (>400 mg/dL [4.5 mmol/L]) or gallbladder disease, oral estrogen should be avoided but transdermal estrogen may be an option. Transdermal estrogen may also be less likely to reduce libido than oral estrogen. Women taking thyroid medication may need dose adjustments.

^dWomen with hysterectomy are candidates for estrogen-alone therapy (ET; TAP HERE to see Tables 2-4 for oral and transdermal ET options). Women with an intact uterus should take combination estrogen plus progestogen (EPT; TAP HERE to see Tables 5-8 for EPT options). FDA-approved bioidentical ET and EPT options are shown in Table 9 (TAP HERE) and pros and cons of different routes of administration of HT are shown in Table 10 (TAP HERE). CE/bazedoxifene (CE with a 3rd generation selective estrogen receptor modulator) is an additional FDA-approved option for women with an intact uterus, especially those with concerns about breast tenderness, breast density, or uterine bleeding (TAP HERE); the contraindications are similar to those for systemic HT (and/or hypersensitivity to its ingredients). Costs of products have a wide range.

^eReassess each step at least once every 6-12 months (assuming patient's continued preference for HT) or if patient's health status changes. Begin with lower doses and, if inadequate symptom relief within 3-6 months, adjust dose or change to different treatment. For duration of treatment decisions, see NAMS HT Position Statement: <http://www.menopause.org/docs/default-document-library/psht12.pdf?sfvrsn=2> and Kautitz AM. Menopause: June 2014 - Volume 21 - Issue 6 - p 679-681. Also see footnotes k and l.

^{f,g} and ^h**Ten-year risk of CVD, based on the ACC/AHA ASCVD Risk Estimator** <http://www.imedicalapps.com/2014/04/ascvd-risk-estimator-app/>
Source: Goff DC, et al, Circ 2013 (reference 10)

Enter information on age, smoking, hypertension diagnosis, systolic blood pressure level, diabetes, total cho-

lesterol, HDL cholesterol: 10-Year atherosclerotic CVD (ASCVD) Risk Score is calculated using the pooled cohorts equation: _____

Enter number of years since last menstrual period: _____

Low^f (<5%) 10-Year CVD Risk and less than 10 years since menopause: Patient appears to be a candidate for either oral or transdermal therapy. Women with hysterectomy can take estrogen-alone therapy (see footnote d and TAP HERE for options and dosages). Women with an intact uterus on HT should take combination estrogen plus progestogen (EPT) (TAP HERE for options and dosages). FDA-approved bioidentical options (TAP HERE) and pros/cons of oral vs transdermal estrogen (TAP HERE) are summarized. Go to footnotes k and l regarding duration of treatment. CE/bazedoxifene (a 3rd generation selective estrogen receptor modulator) is an additional FDA-approved option for women with an intact uterus (dosing: CE 0.45 mg and Bazedoxifene 20 mg daily) (TAP HERE).

Moderate^g (5-10%) 10-Year CVD Risk and less than 10 years since menopause: Patient should avoid oral estrogen, but transdermal estrogen may be an option because it has a less adverse effect on clotting factors, triglyceride levels, and inflammation factors than oral estrogen (TAP HERE to see transdermal options and dosages). TAP HERE to see pros/cons of oral vs transdermal estrogen. TAP HERE to see FDA-approved bio-identical options. Go to footnote k and l regarding duration of treatment.

^gWomen with obesity, diabetes, or metabolic syndrome, if otherwise considered candidates for HT, may do better with transdermal than oral estrogen (TAP HERE to see definition of MetS). Metabolic syndrome is defined as the presence of 3 or more of the following criteria in women: 1) abdominal obesity (waist circumference >35 in [88 cm]); 2) triglycerides \geq 150 mg/dL (1.69 mmol/L); 3) high density lipoprotein cholesterol <50 mg/dL (1.3 mmol/L); 4) blood pressure \geq 130/ \geq 85 mmHg; and 5) fasting glucose \geq 110 mg/dL (6.1 mmol/L) (Adult Treatment Panel III National Cholesterol Education Program 2010).

High^h (>10%) 10-Year CVD Risk: Patient should avoid initiation of systemic hormone therapy. Go to footnote i for non-hormonal treatment options. If the patient has genitourinary symptoms, she may be a candidate for low-dose vaginal estrogen or other treatments (go to footnote b).

^h**Women >10 years past menopause also are generally not good candidates for starting (first use of) systemic HT (go to footnote b and i).** However, decisions about starting or continuing systemic HT beyond age 60 or more than a decade past menopause (or restarting HT in prior users) require individualized decision making and consideration/discussion of the benefit:risk balance (see footnote k and l).

ⁱTAP HERE to see contraindications to SSRIs/SNRIs: hypersensitivity or adverse drug reaction on these medications,

neuroleptic malignant syndrome, serotonin syndrome, and concurrent use of MAO inhibitors. SSRIs/SNRIs should be used with caution in patients with bipolar disease, uncontrolled seizures, hepatic or renal insufficiency, uncontrolled hyponatremia, concurrent use of other SSRIs/SNRIs or, poorly controlled hypertension. May increase suicidal thoughts within the first few months of treatment, although observed primarily in youth and young adults. Preliminary evidence suggests a possible increase in risk of bone fractures. TAP HERE for Paroxetine dosage and other information: Paroxetine 7.5 mg/d (Brisdelle, paroxetine mesylate) is the only SSRI/SNRI currently approved by the FDA for treatment of moderate to severe vasomotor symptoms. Paroxetine and other potent hepatic isoenzyme CYP2D6 inhibitors (e.g., fluoxetine, duloxetine) should be used with caution in women on tamoxifen due to potential reduction in effectiveness of tamoxifen. TAP HERE for information on other SSRIs/SNRIs (off-label use): venlafaxine 75-150 mg/d; escitalopram 10-20 mg/d; citalopram 10-30 mg/day; desvenlafaxine 50 mg/d; paroxetine hydrochloride 10-20 mg/day; paroxetine CR 12.5-25 mg/day; others (similar contraindications but check product labeling). Dosages may need to be adjusted. For severe and resistant symptoms, other less well-established treatments, including stellate ganglion blockade, may be options.

^jTAP HERE for contraindications to, and dosing of, gabapentin, pregabalin and clonidine (off-label use): Gabapentin and pregabalin are contraindicated in patients who have demonstrated hypersensitivity to the drugs or their ingredients. Caution: anticonvulsants may increase suicidal thoughts and behaviors and cause drowsiness, dizziness, and impair balance and coordination. Gabapentin and pregabalin should be dose adjusted in patients with renal insufficiency. Pregabalin may impair memory and concentration. Clonidine is contraindicated in patients with demonstrated hypersensitivity or low blood pressure and may cause lightheadedness, hypotension, headache and constipation; sudden cessation of treatment can be associated with significant rise in blood pressure. Dosing: gabapentin 900-2400 mg/d (dose divided three times per day); pregabalin 150-300 mg/d (dose divided twice per day); clonidine 100 mcg/day. (Dosages may need to be adjusted).

^kand ^lTAP HERE to see information on duration of ET in a patient with hysterectomy and HERE to see information on duration of EPT in a patient with an intact uterus. Decisions about duration of treatment should be individualized and will depend on a number of factors, including patient preference for continuing treatment, persistence of moderate-to-severe menopausal symptoms, and the patient's underlying risk of breast cancer, CVD, osteoporotic fracture, and other conditions. Several other tools, including the Gail Score Estimator for Breast Cancer Risk (<http://www.cancer.gov/bcrisktool/>) and the Fracture Risk Assessment Tool (FRAX; at <http://www.shef.ac.uk/FRAX/tool.aspx?country=9>), may be helpful for these assessments.

NAMS generally recommends treating for the duration of time consistent with treatment goals but avoiding durations longer than 7 years for estrogen-alone and 5 years for EPT (NAMS HT Position Statement: <http://www.menopause.org/docs/default-document-library/psht12.pdf?sfvrsn=2>). However, extended duration treatment may be appropriate in selected patients, such as women at low risk of breast cancer and CVD but at elevated risk of fracture, or patients at low risk who have tried to discontinue treatment but have return of significant symptoms (see below for further discussion: <http://www.menopause.org/docs/default-source/2013/nams-practice-pearl-extended-ht-duration.pdf>)

Algorithm is adapted from: Manson JE, Bassuk SS. The menopause transition and postmenopausal hormone therapy. In: Longo DL, Fauci AS, Kasper DL, Hauser SL, Jameson JL, Loscalzo J, eds. Harrison's principles of internal medicine. McGraw Hill: New York 2011; NAMS Hormone Therapy Position Statement 2012: <http://www.menopause.org/docs/default-document-library/psht12.pdf?sfvrsn=2>); Menopause Practice: A Clinician's Guide, 5th edition, NAMS, 2014, and NAMS website listing of available therapies (<http://www.menopause.org/docs/default-source/2014/nams-ht-tables.pdf>).

Resources and Tables Included in the App:

Summary of lifestyle modifications that can be tried for at least 3 months before considering pharmacologic therapy for vasomotor symptoms: NAMS' MenoNotes on hot flashes (<http://www.menopause.org/docs/for-women/mnflashes.pdf>). Clinician may want to print this out for the patient (or email it via the app) as a handout.

NAMS Hormone Therapy Position Statement, 2012: available at: <http://www.menopause.org/docs/default-document-library/psht12.pdf?sfvrsn=2>.

Personalized Estimation of the 10-Year Atherosclerotic Cardiovascular Disease Risk Score from the American College of Cardiology/American Heart Association (ACC/AHA ASCVD Risk Estimator) <http://www.imedicalapps.com/2014/04/ascvd-risk-estimator-app/>

Source: Goff DC, et al, Circulation 2013 (reference 10 above)

Figure displaying absolute risks of chronic disease outcomes by age group, Women's Health Initiative Hormone Therapy Trials: data from Manson JE, et al. JAMA 2013; 310:1353-1368 (reference 4 above).

NAMS Practice Pearl on Extended Duration Use of Hormone Therapy: Kaunitz A. (available online at: <http://www.menopause.org/docs/default-source/2013/nams-practice-pearl-extended-ht-duration.pdf>)

Several tables adapted from *Menopause Practice: A Clinician's Guide, 5th edition, NAMS, 2014**, including:

Table 1. Vaginal Estrogen Therapy Products for Postmenopausal Use in the United States and Canada (detailed listing of products, composition, and dosages)

- Table 2.** Oral Estrogen Therapy Products for Postmenopausal Use in the United States and Canada (detailed listing of products, composition, and dosages [categories of low, moderate, and high])
- Table 3.** Transdermal Estrogen Therapy Products for Postmenopausal Use in the United States and Canada (patches, gels, emulsions, and sprays: detailed listing of products, composition, and dosages [categories of low, moderate, and high])
- Table 4.** Approximate Equivalent Estrogen Doses for Postmenopausal Use (oral and transdermal formulations)
- Table 5.** Combination Estrogen-Progestogen Therapy Products for Postmenopausal Use in the United States and Canada (*oral continuous-cyclic, oral continuous-combined, oral intermittent-combined, and transdermal continuous-combined regimens*)
- Table 6.** Progestogens Available in the United States and Canada (Detailed listing of products, composition, and dosages)
- Table 7.** Estrogen-Progestogen Therapy Regimens, Terminology (sequential, continuous-combined, intermittent-combined)
- Table 8.** Minimum Progestogen Dosing Requirements for Endometrial Protection With Standard Estrogen Dosing
- Table 9.** FDA-approved “Bioidentical” Hormone Products (FDA-approved products containing estradiol and/or progesterone)
- Table 10.** Pros and Cons of Hormone Therapy Routes of Administration (oral, transdermal, vaginal)

*Note that information on hormone therapy formulations and dosages is regularly updated on the NAMS website at: <http://www.menopause.org/docs/default-source/2014/nams-ht-tables.pdf>.

Disclaimer: This Application is intended for informational purposes only and is not intended as a substitute for professional medical judgment, diagnosis, or treatment. Users of the app are asked to read and accept an End User License Agreement, available on the app.

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