4 – 5 pm

Evaluating the Evidence for Hormone Therapy in Menopausal Women

SPEAKER
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Presenter Disclosure Information

The following relationships exist related to this presentation:

- Pamela Kushner, MD, MA, FAAFP: Consultant for AstraZeneca; Boehringer Ingelheim Pharmaceuticals, Inc.; Bristol-Myers Squibb Company; and Janssen Pharmaceuticals, Inc.. Non-CME honoraria from AstraZeneca and Janssen.

Off-Label/Investigational Discussion

- In accordance with pmiCME policy, faculty have been asked to disclose discussion of unlabeled or unapproved use(s) of drugs or devices during the course of their presentations.

Evaluating the Evidence for Treatment of Menopausal Symptoms

pmiCME

Learning Objectives

- To apply up to date information about the natural history of menopause to improve the care of individual women
- To counsel women about the risks and benefits of systemic hormone therapy for menopausal symptoms, based on their personal risk profile
- To advise women about the relative efficacy, risks, and benefits of commonly used alternatives to systemic hormone therapy for treatment of menopausal symptoms, including:
  - lifestyle changes
  - cognitive behavioral therapy
  - non-hormonal pharmacotherapies
  - newly FDA-approved SERM-based therapies
  - complementary and alternative therapies
  - topical therapies for atrophic vaginitis

Case Presentation

A.R. is a white 52 year old woman with no previous history of hypertension, who presents with complaints of hot flashes, irritability, and diffuse muscle aches after stopping her HT when she heard it causes strokes.

However, a friend who lives in San Diego gave her a copy of a “Harvard Women’s Health Watch” that suggests that since she has a high risk of heart disease, she should take HT. The same friend gave her a local newspaper article quoting famous gynecologists who said the same thing. She asks for your advice.

Case Presentation

Allergies: None

PMHx/PSHx: s/p hysterectomy for fibroids, age 40, ovaries intact

Medications: None

Family History: Mother died of an MI at age 55, father died of an MI at 57. One sister, healthy.

Social History: Married, no children. Works as a lawyer. Has smoked one pack per day for 35 years. Does not drink alcohol. No regular exercise. Eats few fruits and vegetables.

ROS: Vaginal dryness uncomfortable during sex.

Case Presentation

PE: BMI= 30 BP= 139/89 HR= 80, reg., T= 98.6˚F, remainder of the exam unremarkable, except vaginal atrophy.

Labs: TC 244 mg/dL LDL 159 mg/dL HDL 35 mg/dL TG 240 mg/dL, Fasting glucose= 109 mg/dL, A1C = 6.0 Mammogram, Colonoscopy WNL

Estimated 10 year ASCVD risk 9.7%

Case Presentation

- When you return to the room after examining her, she presents you with a list of additional questions, including:
  - I am having trouble with my memory, is it from my menopause?
  - My friend has depression, is it because she is in menopause?
  - Does estrogen cause breast cancer?
  - If I take estrogen, is bioidentical safer?
  - I saw on television that there's a pill for vaginal dryness, should I take it?

Menopause

New Information on Natural History and Associated Symptoms

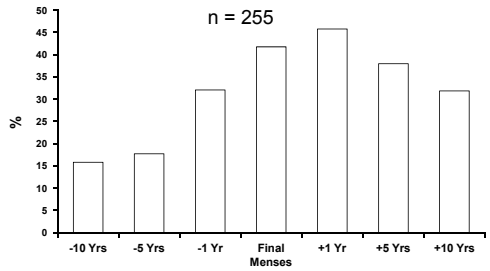
Epidemiology of Vasomotor Symptoms

- Smokers are more likely to experience hot flushes
- African American and Latina patients may be more likely to experience vasomotor symptoms, and experience them for longer than white women
- Higher BMI is associated with a higher likelihood of vasomotor symptoms

Freeman Menopause 2014; Blumel Menopause 2011; Gold Am J Pub Health 2006.

Percent of African American and White Women with Moderate to Severe Hot Flushes:

Penn Ovarian Aging Study
Freeman Menopause 2014



Freeman EW, et al. Menopause 2014, 21:1.

Natural History of Menopause

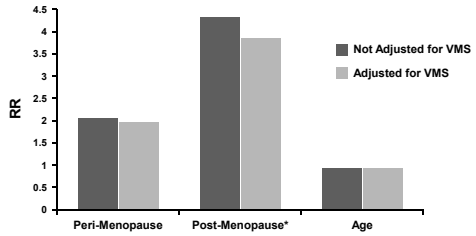
- Systemic symptoms of menopause are not all associated with the degree of vasomotor symptoms
  - Sleep disturbance occurs in women without vasomotor symptoms
  - Cognitive changes reported by some women during the perimenopause improve when the menopause transition is completed
  - Depression is more common during the menopause transition

Kravtiz Obstet Gynecol Clin N Am 2011; Greendale Neurology 2009; Bromberger Psychological Medicine 2011.

Study of Women's Health across the Nation (SWAN):

Major Depression Risk over
10 Years of Follow-up by Menopausal Status or Age

Adjusted for prior major depression, use of psychotropic medications, life events, BMI



*Trend toward decreasing RR more than 2 yrs after menopause.
Adapted from: Bromberger Psychological Medicine 2011.

Vasomotor Symptoms

Hormonal Treatment

Treatment of Menopausal Symptoms: Systemic Hormone Therapy

- Systemic hormone therapy remains the most effective treatment for vasomotor symptoms, with a reduction in symptoms of 80-90% in most studies
- Systemic hormone therapy does not improve health-related quality of life in women without vasomotor symptoms
- Overall risks of hormone therapy are low for otherwise healthy women at the time of menopause
- For women with a uterus, estrogen without a progestin increases the risk of endometrial cancer, and is not recommended in most cases
- Both estrogen and estrogen + progestin increased stroke risk in WHI. Based on this and other risks, long term use of hormones for chronic disease prevention is not recommended.

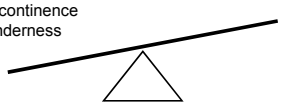
Newton Ann Intern Med 2006; Hess Menopause 2008; Judd JAMA 1996; Manson JAMA 2013; USPSTF Ann Intern Med 2012; ACOG Committee Opinion #565 2013.

Conjugated Equine Estrogens (CEE) and Medroxyprogesterone Acetate (MPA)

Risk-Benefit Balance:
Women's Health Initiative Randomized Clinical Trial During Treatment
(Mean 5.6 years)
Statistically Significant Outcomes

Risks
- Stroke
- Breast Cancer
- DVT/PE
- Dementia (women over 65 years)
- Gallbladder disease
- Urinary incontinence
- Breast tenderness

Benefits
- Osteoporotic fracture
- Diabetes
- Vasomotor symptoms



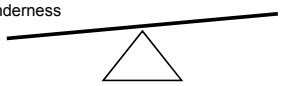
Manson JAMA 2013; Maalouf Arch Intern Med 2010.

CEE Alone

Risk-Benefit Balance:
Women's Health Initiative Randomized Clinical Trial During Treatment
unless Otherwise Noted
(Mean 7.2 years)
Statistically Significant Outcomes

Risks
- Stroke
- DVT/PE
- Gallbladder disease
- Urinary incontinence
- Breast tenderness

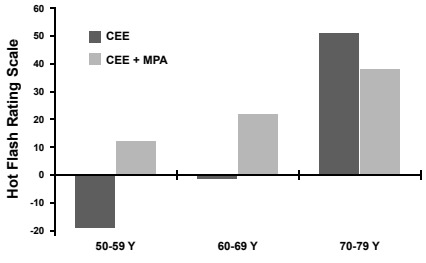
Benefits
- Osteoporotic fracture
- Diabetes
- Vasomotor symptoms
- (Invasive breast cancer after 13 years of follow-up)



Manson JAMA 2013; Maalouf Arch Intern Med 2010.

Global Events per 10,000 Women per Year:

CHD, Invasive Breast, Colon, and Endometrial Cancer,
Hip Fracture, PE, All Cause Mortality



Note: In WHI, all women assigned to CEE alone were s/p hysterectomy

Manson JAMA 2013.

Experts Recommend Avoiding Estrogen Therapy in Breast Cancer Survivors When Possible

- Estrogen plus progestin was associated with increased risk of invasive breast cancer in WHI,
  - But estrogen alone in women with hysterectomy was associated with lower risk.
- However, experts recommend avoiding use of estrogen with or without progestin in breast cancer survivors, because of evidence that the effect of estrogen on established tumors may be problematic
  - Invasive breast cancers in women assigned to CEE in WHI were larger (1.8 cm compared to 1.5 cm, p=.03)
  - Invasive breast cancers in women assigned to CEE in WHI tended to be node positive (36% vs. 23%, p=.07)
  - Aromatase inhibitors, which lower systemic estrogen levels, prevent breast cancer and prevent breast cancer recurrence

Stefanick JAMA 2006; Burstein J Clin Oncol 2014; Visvanathan J Clin Oncol 2013.

What the Experts Are Saying about Hormone Therapy

- American College of Obstetricians and Gynecologists **(ACOG)**
  - "Menopausal HT should not be used for the primary or secondary prevention of CHD at the present time."
  - "Recent evidence suggests that women in early menopause who are in good cardiovascular health are at low risk of adverse cardiac outcomes and should be considered candidates (for HT) for relief of menopausal symptoms."
- U.S. Preventative Services Task Force **(USPSTF)**
  - The USPSTF recommends against the use of combined estrogen and progestin for the prevention of chronic conditions in postmenopausal women (Grade D: Evidence of Harm)
  - The USPSTF recommends against the use of estrogen for the prevention of chronic conditions in postmenopausal women who have had a hysterectomy (Grade D: Evidence of Harm)

ACOG Committee Opinion #565 2013; USPSTF Ann Intern Med 2012.

Principles of Hormone Treatment

- Guidelines recommend the "lowest effective dose", although different doses have not been comparatively studied, this seems a prudent approach
- Very important to add progestin in women with a uterus
  - One third of women on unopposed estrogen develop advanced hyperplasia after 3 years of treatment
- Some clinicians are offering women with a uterus placement of a levonorgestrel IUD instead of a systemic progestin to balance systemic estrogen use, this is an "off label" use which is not FDA approved
  - Given the very low risk of adverse events from use of progestins, most experts do not recommend this

Judd JAMA 1996.

FDA Takes Action against Compounded Hormone Therapy Drugs ("Bioidenticals")

- Risks of compounded bioidenticals unknown
  - No evidence of greater safety, efficacy
  - Estriol not FDA approved
- Saliva testing to determine hormone levels is inaccurate
  - Hormone levels fluctuate

Source: FDA Press Release, January 9, 2008.

American College of Obstetricians and Gynecologists Committee Opinion August 2012

"Not only is evidence lacking to support superiority claims of compounded bioidentical hormones over conventional menopausal hormone therapy, but these claims also pose the additional risks of variable purity and potency and lack efficacy and safety data"

- Under and overdosage are of concern, eg. endometrial hyperplasia and cancer are a concern with untested/unreliable doses of estrogen and progestins
- Estradiol and micronized progesterone are available in proven formulations, and are preferred given available data

ACOG Committee Opinion #532 2012.

Newly FDA approved for Treatment of Vasomotor Symptoms in Women with a Uterus

- Conjugated equine estrogens/bazedoxifene (Duavee®)
  - Estrogen with new SERM, approved by FDA in 2013 for treatment of vasomotor symptoms and prevention of osteoporosis in women with a uterus
  - Boxed warning: risk of endometrial cancer, stroke, DVT, dementia, do not use for prevention of dementia OR CHD. Also, do not use if breast or other estrogen-dependent cancer, pregnancy.
    - 24 months of endometrial safety data, over 24 months increased hip and spine BMD, effect on hot flushes similar range to estrogen
    - Studies lacked power (6200 patients over max 2 years) to adequately assess stroke and DVT, but increased risk known for HT and other SERMS; breast cancer effects unknown
    - About 15% of patients spotting at one year
  - Dose CEE 0.45 mg/bazedoxifene 20 mg, one po daily; given limited data, an alternative to traditional estrogen plus progestin therapy for hot flushes, but not proven to be safer/better than estrogen plus progestin

Vasomotor Symptoms

Non-Hormonal Treatment

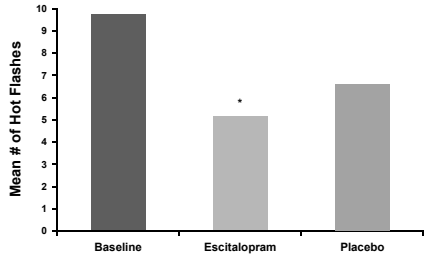
Nonhormonal Pharmaceuticals for Hot Flushes More Effective Than Placebo in Randomized, Controlled Trials: Lowest Effective Dose, **non-FDA Approved Use Unless Noted**

- SNRIs: Venlafaxine; Desvenlafaxine
- SSRIs (avoid in patients on tamoxifen as may inhibit CYP2D6 and reduce metabolism to active metabolite): Paroxetine (Brisdelle (R) 7.5 mg FDA approved); Fluoxetine; Sertraline; Citalopram; Escitalopram
- Anti-seizure medications: Gabapentin, Pregabalin
- Anti-hypertensives: Clonidine

Loprinzi Lancet Oncology 2008; Loprinzi J Clin Oncol 2010; ACOG Practice Bulletin #141 Obstet Gynecol 2014.

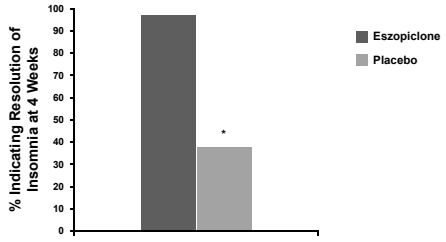
Escitalopram for Hot Flushes in Healthy Menopausal Women:

A Randomized Controlled Trial



*Statistically fewer hot flushes than placebo.
Freeman JAMA 2011.

Anxiolytics for Hot Flush-Related Sleep Disturbance



* p < 0.0001
Adapted from Joffe Am J Obstet Gynecol 2010.

Vasomotor Symptoms

Alternative and Complementary Therapies

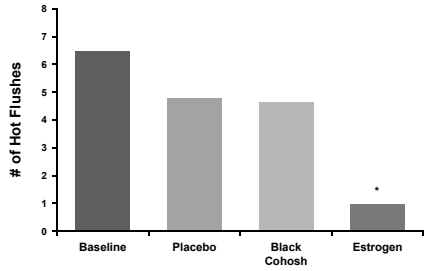
Common Complementary Treatments for Vasomotor Symptoms Studied in at Least One Randomized, Controlled Trial

- Soy
- Vitamin E
- Black Cohosh
- Dong Quai
- Red Clover
- Ginseng
- St John's Wort
- Ginko Biloba
- Acupuncture

ACOG Practice Bulletin #141 2014.

Treatment of Vasomotor Symptoms with Black Cohosh, Multibotanicals, Soy, Hormone Therapy, or Placebo:

Selected Results at 3 Months Compared to Baseline



* Statistically significantly lower than placebo.
Adapted from Newton Ann Intern Med 2006.

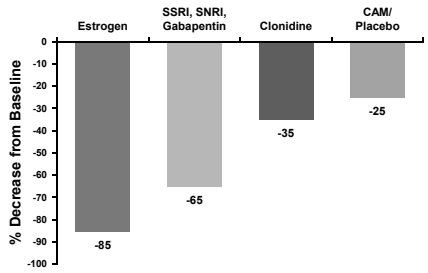
The Placebo Effect and Hot Flushes

- Efficacy of alternative and complementary therapies is similar to placebo
- Placebo benefit is a 25%-50% reduction in vasomotor symptoms
- *"We feel that some of the dramatic results achieved with preparations such as vitamin E and a famous vegetable compound now on the market must be attributed to the psychological effect of a placebo…"*

—Kupperman, et al, JAMA 1959,
as quoted by Nancy King Reame, Menopause 2005

ACOG Committee Opinion #141 2014; Leach Cochrane Database Syst Rev 2012; Lethaby Cochrane Database Syst Rev 2013; Dodin Cochrane Database Syst Rev 2013; Reame Menopause 2005.

Menopause: Hot Flushes and Associated Symptoms



An Intensive Behavioral Weight Loss Intervention and Hot Flushes in Women

338 overweight or obese women enrolled in a 6 month randomized controlled trail of an intensive behavioral weight loss intervention compared to a structured educational program to promote weight loss to improve urinary incontinence completed a self-administered questionnaire assessing hot flushes.

- 154 women endorsed that they were bothered by hot flushes at the start of the study.
- Reductions in weight (OR 1.32, 95% CI 1.08-1.61 per 5 kg decrease), BMI (OR 1.17, 95% CI 1.05-1.30 per 1 point decrease), and abdominal circumference (OR 1.32, 95% CI 1.07-1.64 per 5 cm decrease) were associated with a 1 point improvement in a five point self-reported hot flash scale.
- Changes in physical activity, calorie intake, blood pressure, and physical and mental functioning were not associated with a change in hot flush symptoms

Haung Arch Intern Med 2010; Daley Cochrane Database Syst Rev 2011.

Vasomotor Symptoms

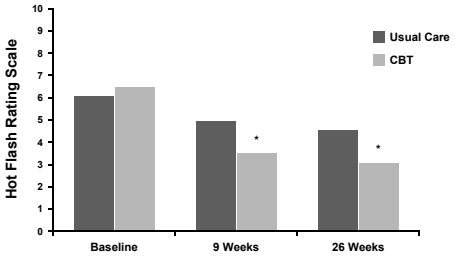
Stopping Menopause Hormone Therapy

Factors Associated with Successful Discontinuation of Hormone Therapy

- Survey of 1,358 women on HT at Group Health, Washington State, Harvard Vanguard Medical Associates in Massachusetts, 802 attempted discontinuation, mean age 57 years, 91% white
  - Factors associated with successful discontinuation:
    - Lack of symptom improvement with HT OR 4.21
    - Vaginal bleeding OR 5.96
    - Doctor's advice OR 2.62
    - Learning to cope with symptoms OR 3.36
  - Factors associated with unsuccessful discontinuation:
    - Trouble sleeping OR 0.40
    - Mood swings/depression OR 0.63
- A randomized trial of tapering versus abrupt discontinuation found tapering did not improve health related quality of life or improve quit rates

Newton J Women's Health 2014; Lindh-Astrand Menopause 2010.

6 Weeks of Weekly Cognitive Behavioral Therapy Improves Quality of Life for Women with Hot Flushes and Night Sweats



* Statistically better mood, sleep, quality of life. No significant difference in hot flash frequency.
Mann Lancet Oncol 2012.

Dyspareunia and Sexual Dysfunction

Etiology and Treatment

Treatment of Vaginal Atrophy

- Vaginal lubricants and moisturizers
- Local hormone therapies- more effective, progestins not required when used at local doses, preferred to systemic therapies for women with only vaginal symptoms
  - Estradiol vaginal ring (2 mg) (Estring®): Insert q 12 weeks
  - Estradiol vaginal tables (Vagifem®) Insert 10 mcg nightly x 14 days, then biw
  - "Low dose" topical estrogen
    - Cochrane review found ? more risk of endometrial hyperplasia, CEE vaginal cream .5 gm biw studied for one year
- Systemic hormone therapy
  - Only indicated if also used for vasomotor symptoms, increases urinary incontinence
- Systemic ospemifene (estrogen agonist/antagonist)
  - Recently FDA approved, increases hot flushes, long term safety not known

ACOG Committee Opinion #141 2014; Suckling Cochrane Database Syst Rev 2006.

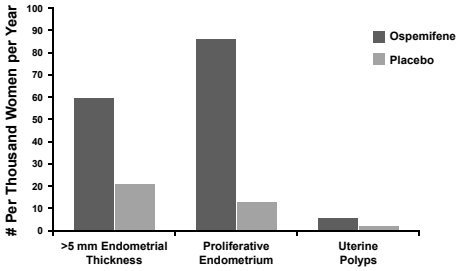
Newly FDA Approved for Treatment of Vaginal Atrophy

- Ospemifene (Osphena®)
  - Estrogen agonist/antagonist (SERM) approved in 2013 by the FDA for treatment of moderate to severe dyspareunia
  - Increases hot flushes; Boxed Warning: risk of endometrial cancer, stroke, DVT, Contraindications: pregnancy, known or suspected estrogen-dependent neoplasia, MI, use of estrogen, another SERM
    - 52 week study of endometrial safety showed RR 3 for endometrial thickening and polyps and RR 6 for proliferative endometrium, with estrogens and SERMS risk known to increase with duration of use; ? need for progestin if used longer term (not studied)
    - Studies lacked power to adequately assess stroke and DVT, but increased risk known for HT and other SERMS (only 409 women studied for one year or more)
    - Breast cancer, osteoporosis effects unknown
  - Dose 60 mg daily with food, based on limited safety data and availability of well studied topical therapy, would possibly consider in refractory cases, significant concerns for longer term use in women with a uterus

FDA 2013; ACOG Committee Opinion #141 2014.

Ospemifene FDA Warning Regarding Risk of Endometrial Cancer:

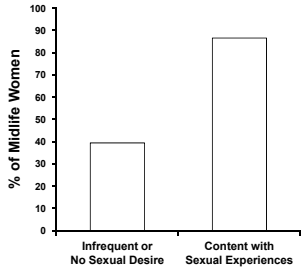
Approval Based on 12-15 Months of Follow-up in 409 Women



FDA 2013.

Study of Women's Health Across the Nation:

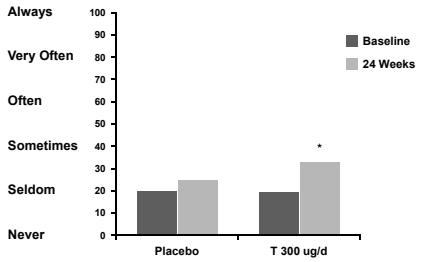
Although Many Women Have Infrequent or Low Sexual Desire, Most Are Content with Sexual Experiences



Basson NEJM 2006.

Testosterone for Low Libido in Postmenopausal Women Not Taking Estrogen:

Mean Scores on Sexual Desire Domain of Profile of Female Sexual Function did not Achieve "Sometimes"



*1.4 more satisfying sexual encounters/month $p < 0.001$.
Davis NEJM 2008.

Expert Guidelines on Testosterone Therapy in Women

ACOG 2011:

- **Level A:** "Transdermal testosterone has been shown to be effective for the short-term treatment of hypoactive sexual desire disorder, with little evidence to support long term use" (not FDA approved)
- **Level B:** "The main risks associated with androgen replacement.. are hirsutism, acne, virilization.. cardiovascular complications, [and] a possible association with breast cancer.
- **Level C:** "There is no proven clinical utility to monitoring androgen levels before or during treatment for hypoactive sexual desire disorder [in women]"

Endocrine Society 2014:

- "We recommend against making a diagnosis of androgen deficiency syndrome in healthy women.. we recommend against the routine prescription of testosterone for.. surgical menopause or ..low androgen levels"
- "Evidence supports short-term efficacy of [testosterone] for hypoactive sexual desire disorder ... testosterone levels do not predict response ... long-term safety data are lacking (preparation for women not available in U.S.)"

ACOG Practice Bulletin # 119 2011; Wierman J Clin Endorinol Metab 2014.

Summary: Evaluating the Evidence for Treatment of Menopausal Symptoms

Epidemiology

- Moderate to severe hot flashes affect nearly half of women during the menopause transition, and often are present for 10 or more years
- The risk of major depression is heightened during the menopause transition

Hormone therapy

- Hormone therapy is not recommended for chronic disease prevention
- Systemic hormone therapy is the most effective treatment available for vasomotor symptoms
- Overall risks of hormone therapy for symptoms are low for otherwise healthy women
- For women with a uterus, progestins should be given to avoid endometrial cancer
- When choosing hormone therapy, women should be aware of increased risk of stroke, venous thromboembolism, and, if they are taking a progestin, breast cancer
- Risks of hormone therapy increase with age

Summary: Evaluating the Evidence for Treatment of Menopausal Symptoms

Non-hormonal treatment for vasomotor symptoms

- SNRIs, SSRIs, and gabapentin are commonly used pharmacotherapies to treat vasomotor symptoms
- Anxiolytic sleep aids are effective in improving menopause-related insomnia
- Cognitive behavioral therapy improves quality of life in women with hot flushes
- Alternative and complementary therapies are similar to placebo in reducing hot flushes. This is a 25% to 50% reduction in symptoms in most studies.
- Weight loss improves hot flushes

Treatment of vaginal atrophy

- Topical treatments are efficacious and preferred as first line therapy
- Local estrogen treatments can be used without systemic progestins
- Systemic treatments include hormone therapy (when also used for vasomotor symptoms) and ospemifene (an estrogen agonist/antagonist). Ospemifene increases hot flushes, and concerns remain about endometrial hyperplasia with longer term (greater than 15 month) use, as this has not been studied.