HOT FLASHES/MENOPAUSAL SYMPTOMS

Common in post and peri-menopausal women.
Prevalence increased in women with breast cancer.
Often occur earlier in women with breast cancer.
Affects 50 - 88 % of men with prostate cancer.
A hot flash is characterized by the sudden onset of a sensation of intense warmth that begins in the chest and may progress to the neck and face.
Hot flashes are generally associated with vasodilation and a drop in core body temperature.
They may be accompanied by sweating, flushing, palpitations, anxiety, irritability and are sometimes followed by chills.
Average hot flash lasts ~ 4 minutes, although they can be as long as 20 minutes.

PATHOPHYSIOLOGY OF HOT FLASHES

In peri-menopausal women, the occurrence is concordant with hormonal changes, and flushes are considered to be due to changes in estrogen levels, particularly estrogen withdrawal.
Changes in estrogen levels may affect functioning of thermoregulatory centers in the hypothalamus.
Central thermoregulatory centers maintain core body temperatures within a normal range (thermoneutral zone).
If the body temperature exceeds the upper threshold, perspiration and peripheral vasodilation occur. Conversely, a body temperature below the lower threshold induces shivering.
In postmenopausal women reporting frequent hit flashes, the core body "sweating threshold" has been shown to be lower than in asymptomatic women.
Thermoregulatory centers appear to be influenced by changing estrogen concentrations via direct and indirect pathways.

Indirect pathways may act via changes in neurotransmitter levels:

Primary neurotransmitters are norepinephrine and serotonin.

HOT FLASHES IN BREAST CANCER PATIENTS

Hot flashes have been reported in up to 65% of postmenopausal patients with breast cancer.
Postmenopausal women treated for breast cancer appear to have a higher incidence of hot flashes compared to healthy postmenopausal women.
Breast cancer patients appear to experience more vasomotor symptoms.
Hot flashes appear to last longer in breast cancer patients.
Causes of hot flashes/menopausal symptoms in breast cancer patients include chemotherapy and hormonal therapy (with antiestrogens, LHRH analogs, and aromatase inhibitors).

MANAGEMENT OF HOT FLASHES

In otherwise healthy women, hot flashes can be treated with systemic hormonal therapy (estrogen alone or combined with progesterone).
Estrogen therapy decreases hot flashes by 80 – 90% and is considered the most effective therapy.
Because of breast cancer risk, the only indication for hormonal therapy in healthy women is for hot flashes that severely compromise a woman's quality of life.
Hormonal therapy should be avoided in women with a history of breast cancer.

NON-HORMONAL THERAPY OF HOT FLASHES

NOTE: There appears to be a significant placebo effect associated with the treatment of hot flashes. Reductions in hot flashes of 25 – 40% are consistently reported in patients randomized to placebo therapy, and effects can persist for several weeks. The FDA recommendations are that treatments for hot flashes be studied for at least 12 weeks.

PHARMACOLOGIC AGENTS: PRESCRIPTION

CLASS/DRUG	DOSE	COMMENTS
Serotonin-Norepinephrine Reuptake Inhibitors (SNRIs) Venlafaxine (Effexor®)	37.5 mg/day initially, ↑ to 75 mg/day	Higher doses associated with increased side effects.
Selective Serotonin Reuptake Inhibitors (SSRIs) Fluoxetine (Prozac®) Paroxetine (Paxil®) Sertraline (Zoloft®) Citalopram (Celexa®)	 20 mg/day 10 – 20 mg/day 50 mg/day 10 – 20 mg/day	SSRIs can inhibit CYP 2D6, which converts tamoxifen to endoxifen and 4-hydroxy-tamoxifen, both of which are active metabolites. Avoid in patients taking tamoxifen. Side Effects: sexual dysfunction, nausea, anxiety/nervousness.
Clonidine	0.1 mg/day	Oral and transdermal. Risk of rebound hypertension with sudden discontinuation.
Gabapentin (Neurontin®)	900 mg/day	May start at lower dose and titrate up to minimize side effects. Not well-tolerated, with ~ 50% of patients reporting at least one adverse event.
Belladonna and phenobarbital (Bellergal®/Bellergal-S®)		In trials, benefit slight and of short duration. ? Not available in US.

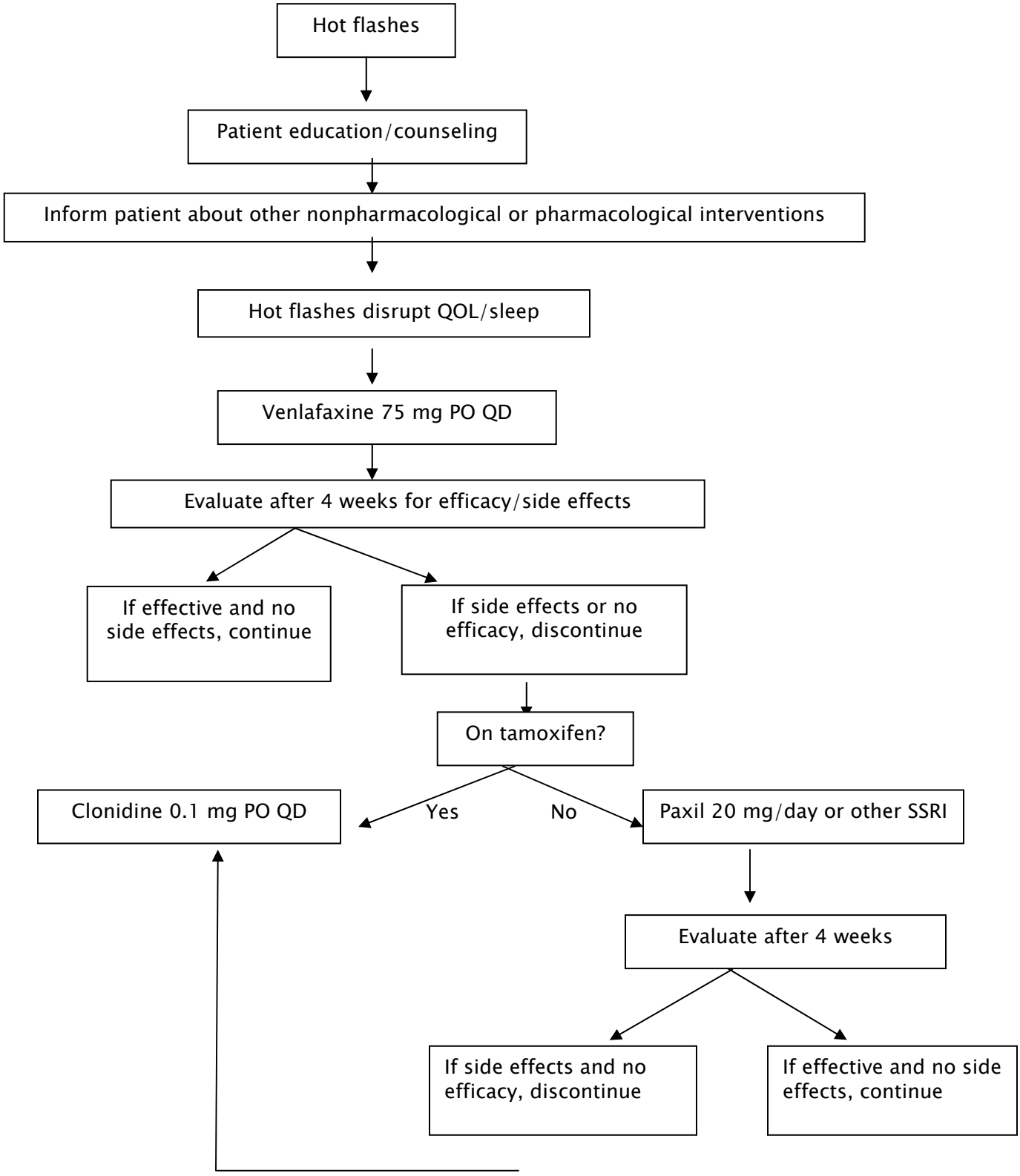
PHARMACOLOGIC AGENTS: NON-PRESCRIPTION	
Agents	**Comments**
Vitamin E	800 international units/day. Anecdotal data. Placebo effect?
Phytoestrogens Isoflavones (most common) Lignans	Have estrogen or antiestrogen effects, depending on ambient estradiol concentrations, gender, and menopausal status. Studies comparing isoflavones (90 or 150 mg/day) showed no benefit over placebo. Safety in breast cancer patients uncertain.
Black Cohosh (*Cimicifuga racemosa*)	Herbal remedy for gynecologic/other conditions. Randomized trials show no benefit over placebo.
Evening Primrose Oil	Lineoleic acid may have phytoestrogenic activity? Anecdotal evidence only.
Homeopathic remedies individualized single remedies Hyland's Menopause® (combination product: Amyl nitrate 3X (1:10000 dilution), Sanguinaria Canadensis 3X, and Lachesis 12X (1:1,000,000,000,000 dilution)	Observational data suggests improvements in symptom scores. Randomized, placebo-controlled study showed no benefit vs. placebo.

NON-PHARMACOLOGIC MANAGEMENT OF HOT FLASHES

Cooling approaches: wear light clothes, lower room temperature, and cool beverages.
Behavioral interventions:
- Reduce stress: yoga, meditation, massage, paced breathing.

Avoid triggers: stress, caffeine, alcohol, spicy foods, and hot beverages.
Exercise: aerobic and weight-bearing.
Acupuncture: better than placebo in controlled studies, but less effective than estrogen:
- Likely to be safe if sterile needles used;
- Avoid acupuncture to affected arm.

ALGORITHM FOR TREATMENT OF HOT FLASHES



Adapted from: Boekhout AE, Beijnen JH and Schellens JHM. *Oncologist* 2006;11:641 – 54.

Last Updated on January 17, 2007

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