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9TH EUROPEAN CONGRESS ON MENOPAUSE AND ANDROPAUSE ATHENS, GREECE, 28-31 MARCH, 2012



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EMAS ATHENS 2012

Upholding Menopausal Health

Join global opinion leaders and colleagues in Athens for EMAS 2012 - the 9th inspiring and multi-disciplinary Menopause and Andropause conference. Organised by the European Menopause and Andropause Society (EMAS) and hosted by the Hellenic Society for the Study of Climacterium and Menopause, the congress will explore current problems and the latest advances in the field.

In keeping with the congress theme "Upholding Menopausal Health," an advanced scientific programme will provide an in-depth look at healthy aging.

Register early and help shape the future of menopause in Europe!

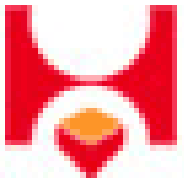
Upholding Menopausal Health



ORGANISED BY THE
EUROPEAN MENOPAUSE
AND ANDROPAUSE
SOCIETY (EMAS)

HOSTED BY THE
HELLENIC SOCIETY FOR THE
STUDY OF CLIMACTERIUM
AND MENOPAUSE





CHU Saint-Pierre



UNIVERSITÉ LIBRE DE BRUXELLES,
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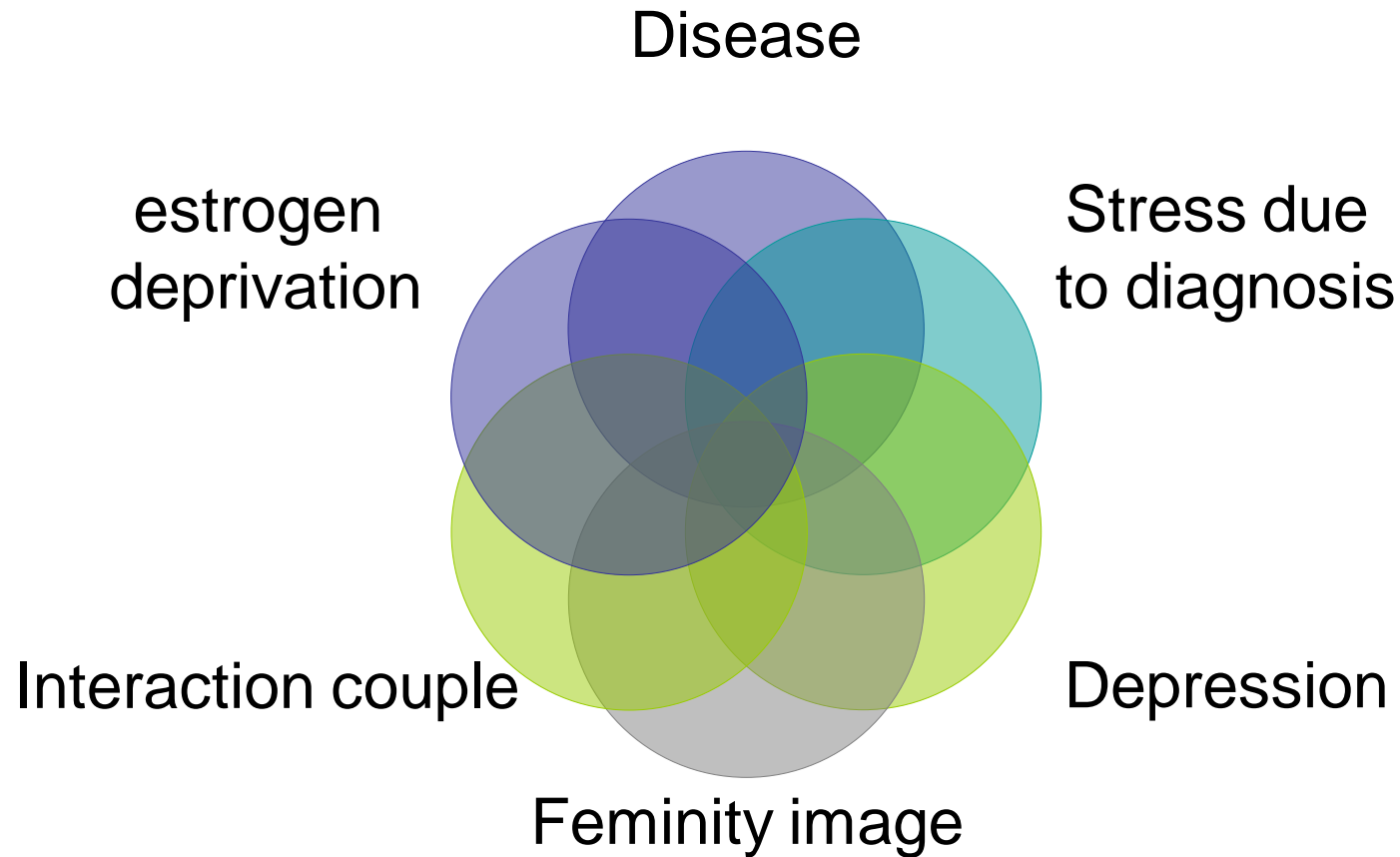
Treatment of menopausal symptoms in breast cancer survivors IMS Rome 2011

Serge Rozenberg

Department of Obstetrics and gynaecology
CHU ST Pierre (ULB). Rue haute 290, 1000
Brussels, Belgium

EMAS president

Increased menopausal (sexual) symptoms in BRCA survivors



Ovarian failure

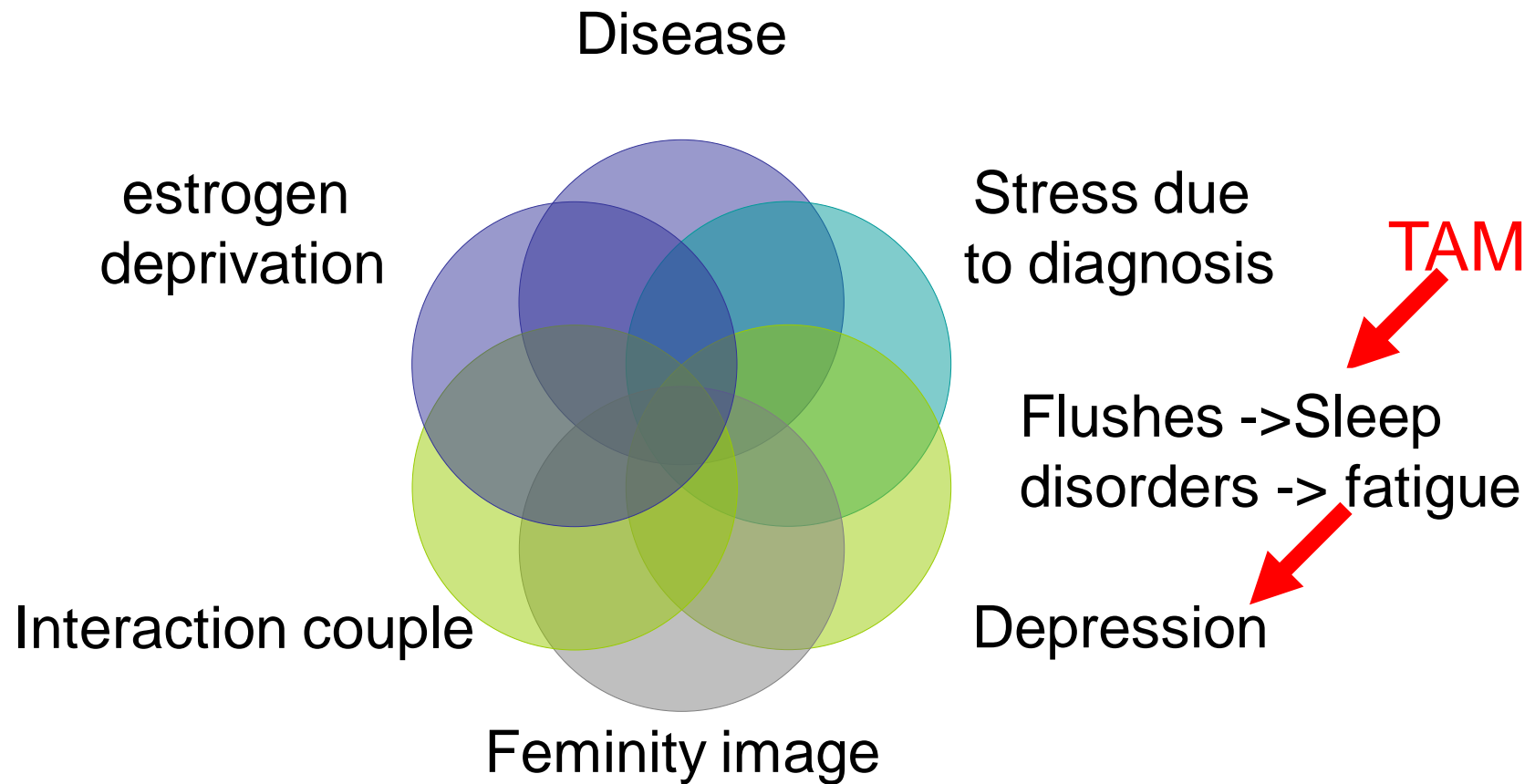
TABLE 3. INCIDENCE OF AMENORRHEA AFTER COMMON ADJUVANT TREATMENTS FOR BREAST CANCER.

TREATMENT AND DURATION	AGE OF	AGE OF	AGE OF
	<30 YR	30–39 YR	>40 YR
	percent with amenorrhea		
None	0	4–6	20–25
Tamoxifen ⁴²	0	<5	5–30
Cyclophosphamide, methotrexate, fluorouracil (6 mo) ⁴³	19	30–40	80–95
Fluorouracil, doxorubicin, cyclophosphamide or fluorouracil, epirubicin, cyclophosphamide (3–6 mo) ^{38,44}	0	10–25	80–90
Doxorubicin and cyclophosphamide (3 mo) ^{43,45}	—*	13	57–63

*No data have been reported on the incidence of amenorrhea among patients younger than 30 years of age who have received doxorubicin and cyclophosphamide.

- develops within one year of therapy in 63%–96% of premenopausal women, receiving chemotherapy
- It is in many cases definitive

Increased menopausal symptoms in BR CA survivors



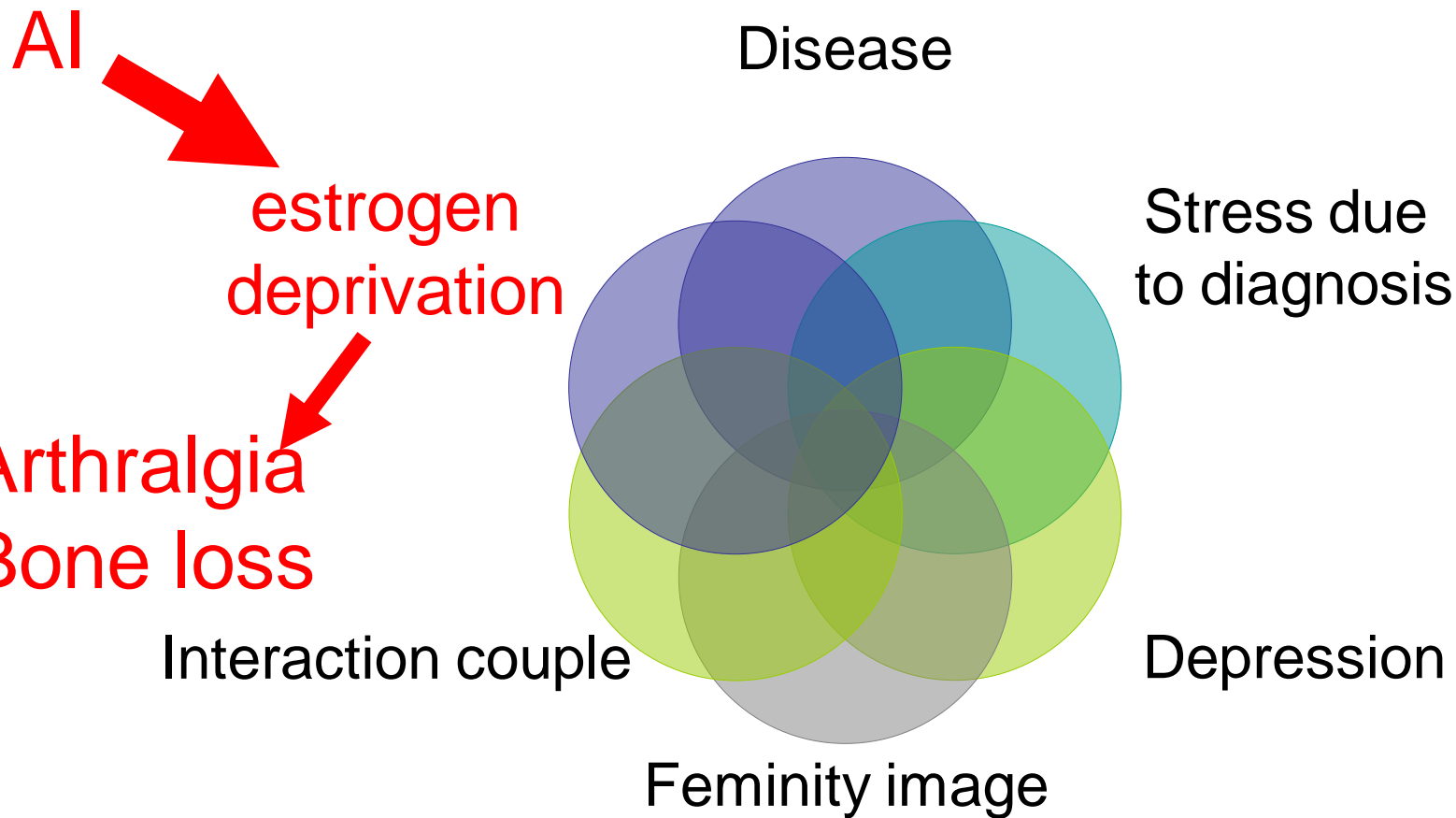
Prevalence and Treatment of Menopausal Symptoms Among Breast Cancer Survivors

	Controls	Breast Cancer Cases				OR ^b	95% CI	
	<i>n</i> = 73	All cases <i>n</i> = 110	OR ^a	95% CI	No Tamoxifen <i>n</i> = 48			Tamoxifen <i>n</i> = 62
Any menopausal symptom	32%	73%	5.3	2.7–10.2	63%	81%	2.6	1.1 –6.25
Under age 55 (<i>n</i> = 88)	42 (<i>n</i> = 11)	77 (<i>n</i> = 48)	17.5	4.0–77	65 (<i>n</i> = 20)	90 (<i>n</i> = 28)	6.4	1.4 –29.4
Age 55 and over (<i>n</i> = 95)	28 (<i>n</i> = 13)	7 (<i>n</i> = 32)	6.8	2.5–18.2	9 (<i>n</i> = 10)	71 (<i>n</i> = 22)	1.9	0.6 –6.9
Of those with symptoms								
Hot flashes	83%	96	6.0	1.2–33	97	96	0.7	0.1 –8.6
Insomnia	42	38	0.78	0.3–2.0	40	36	0.8	0.3 –2.2
Vaginal dryness	0	6	—	—	7	6	0.9	0.1 –5.6
Mood swings	8	14	1.5	0.3–7.5	27	6	0.18	0.04–0.74
Other (weight gain, fatigue)	0	4	—	—	3	6	2.1	0.20–21

5-17 X

3-6 X

Multiple reasons for sexual problems in BR CA survivors



Survey among breast cancer survivors

- Current users of **aromatase inhibitors**
significant increases ($\pm \times 2$)
 - sexual disorders (65%)
 - unsatisfactory sexual life (55%)
 - vaginal dryness (88%)
 - decreased libido (84 %)
- Antoine et al Climacteric 2008

Survey among breast cancer survivors

- About a quarter used a treatment to alleviate menopausal symptoms

Antoine et al Climacteric 2008

Survey among breast cancer survivors

- A third of symptomatic women did not use no therapy

Antoine et al Climacteric 2008

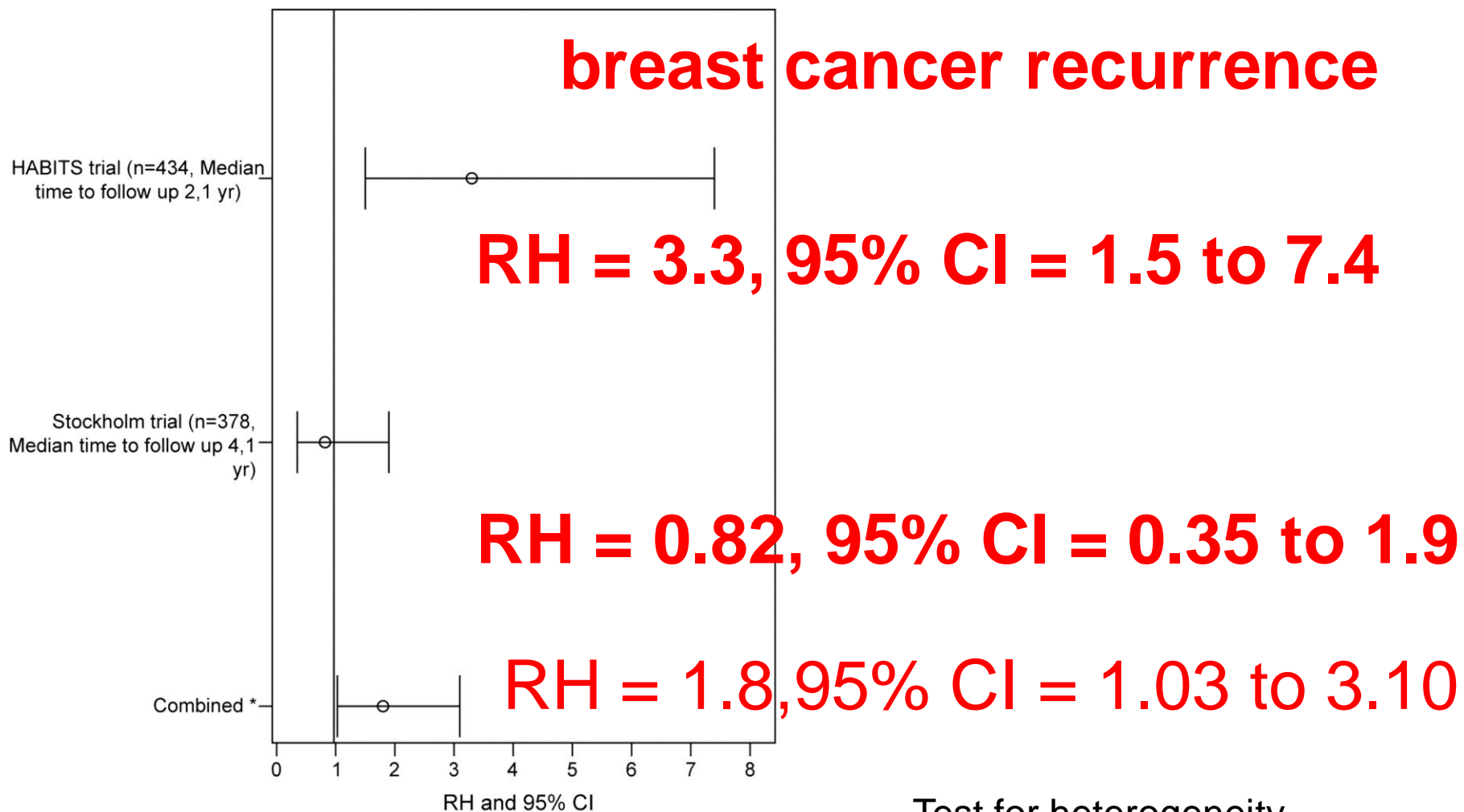
Up to 20% consider stopping or
ceased endocrine treatment
because of menopausal
symptoms
Fellows et al 2001.

Oestrogen deficiency after Breast Cancer

- Vasomotor symptoms
- Vaginal dryness and sexual problems
- Osteoporosis
- Cognitive function

Summary of the two randomized trials that have been conducted

breast cancer recurrence



Test for heterogeneity between the two studies ($P = .02$),

Kennemans et al Liberate Lancet Oncol. 2009

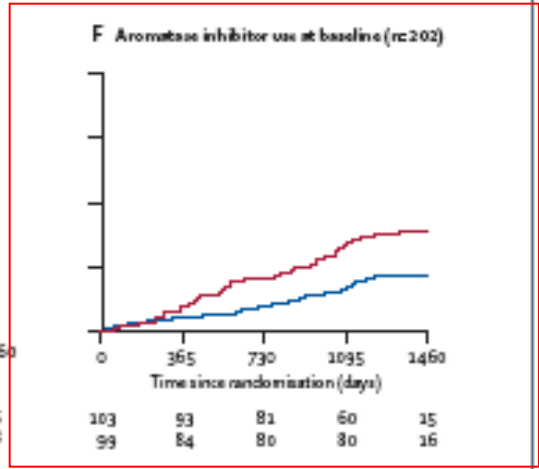
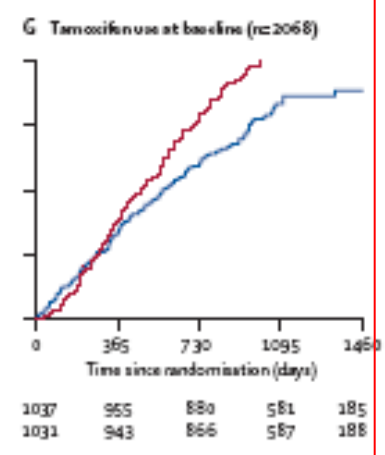
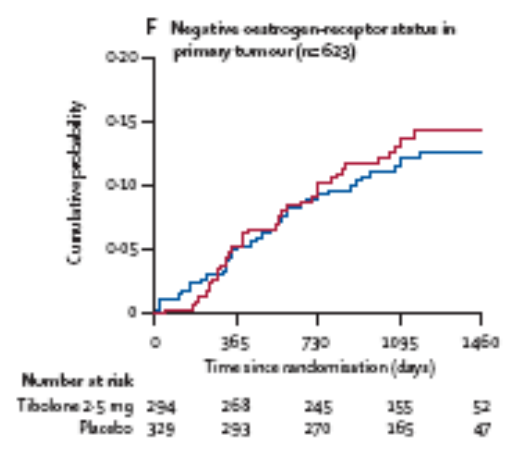
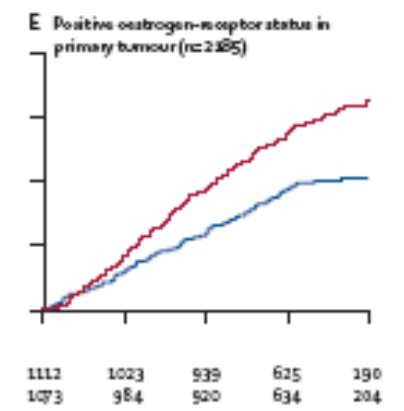
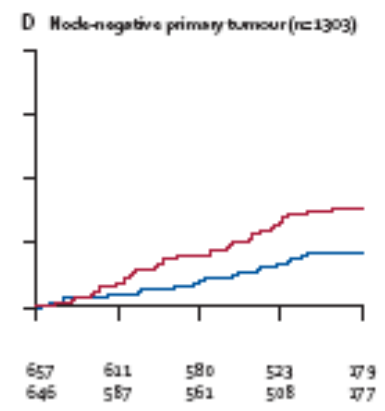
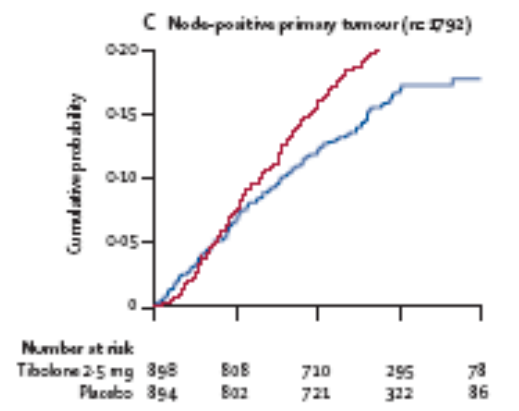
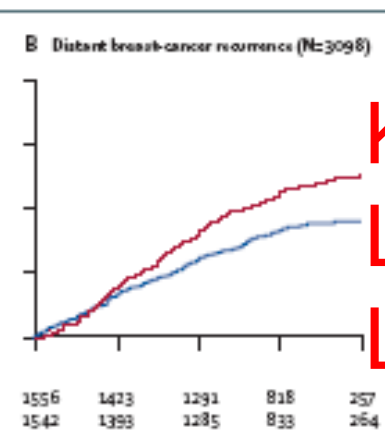
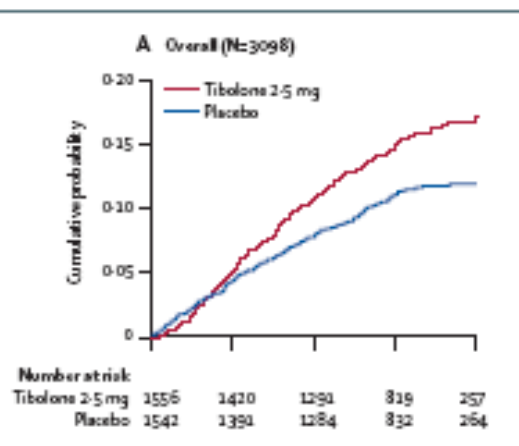
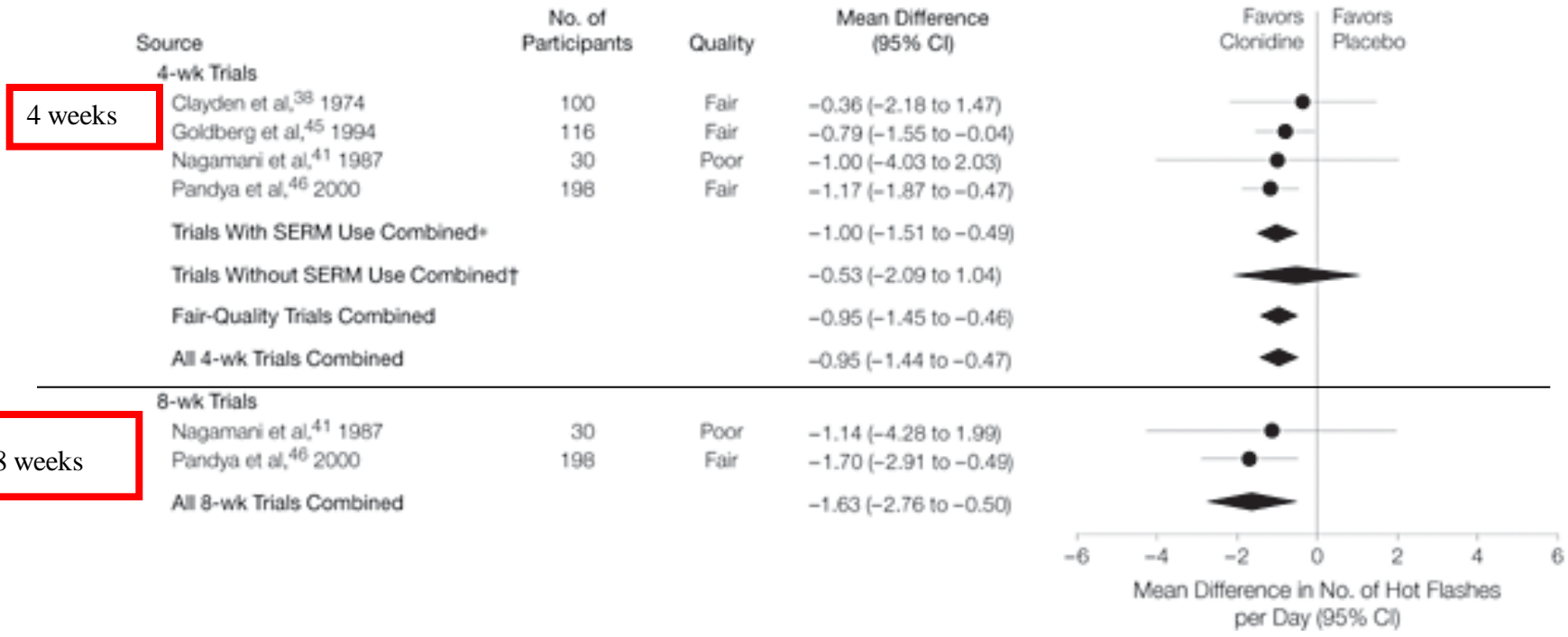


Figure 2: Cumulative probability of breast-cancer recurrence versus time in the ITT population

Neuroendocrine agents

- Recognition of a neuroendocrine role in hot flashes
 - Antidopaminergic (methyldopa and veralipride)
 - α -adrenergic-receptor agonists (clonidine)
- have not been tested in clinical trials in patients with breast cancer.

Metaanalysis of Clonidine



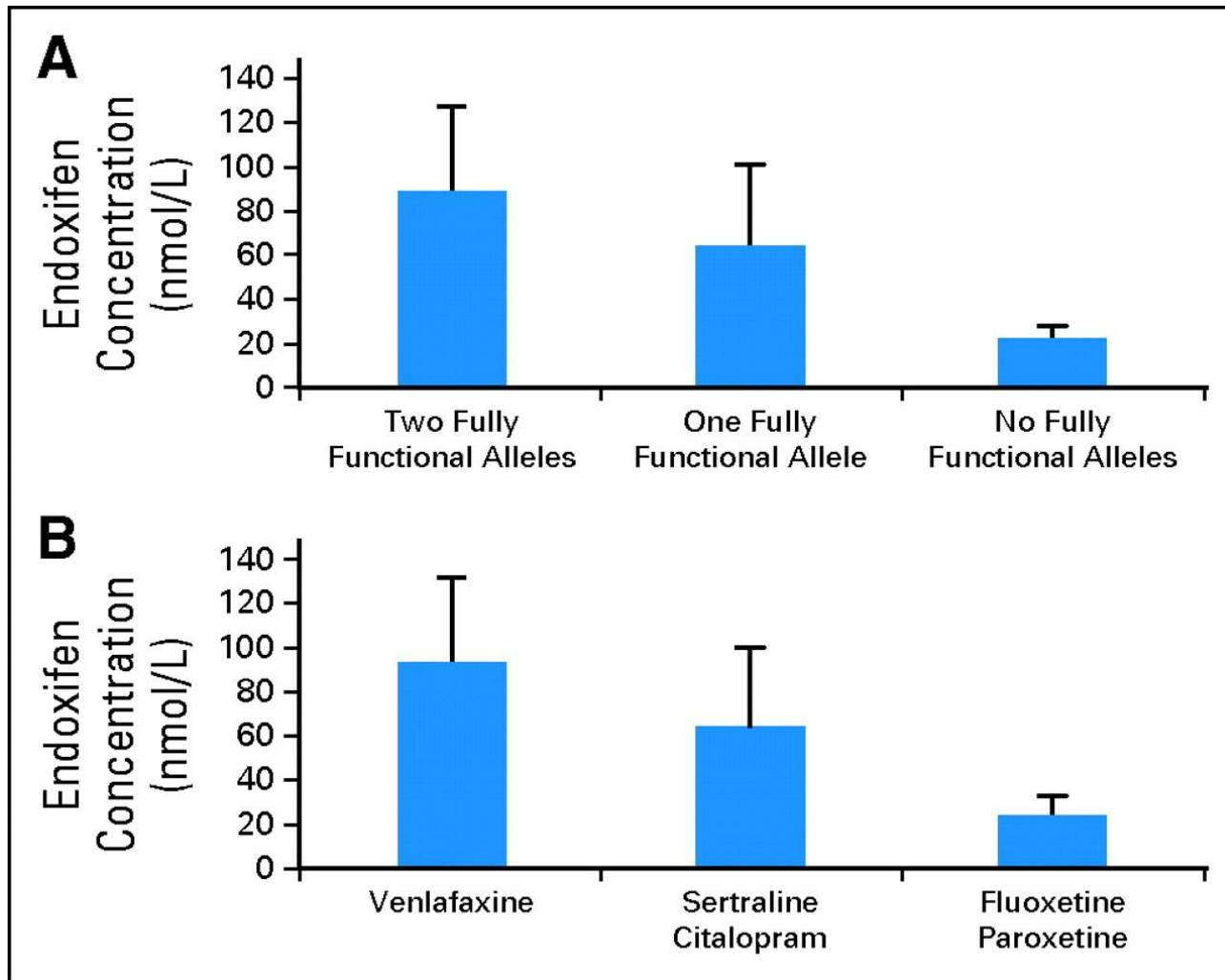
4 weeks

8 weeks

New antidepressants

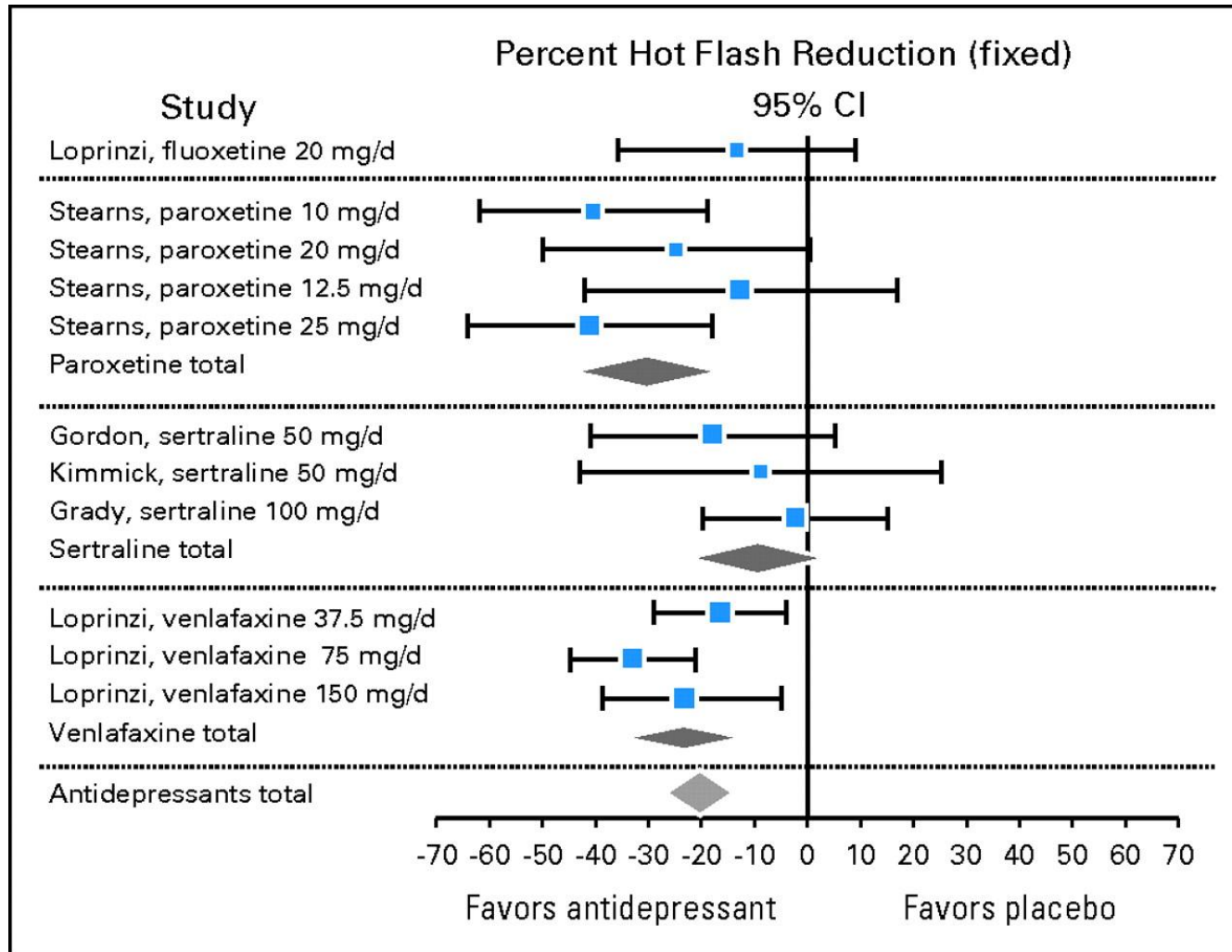
- affecting serotonin and/or norepinephrine concentrations
 - Venlafaxine
 - Desvenlafaxine
 - Fluoxetine
 - Citalopram
 - Sertraline
 - and paroxetine.

Endoxifen concentration according to CYP2D6 activity.



Sideras K et al. JCO 2010;28:2768-2776

Forest plots of hot flash reduction in newer antidepressant studies.

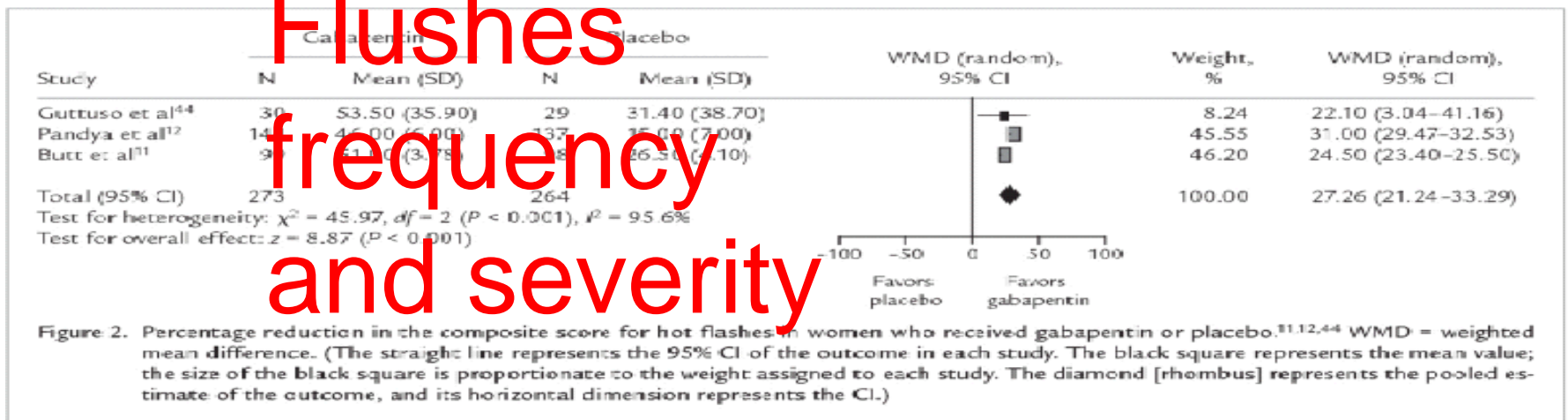
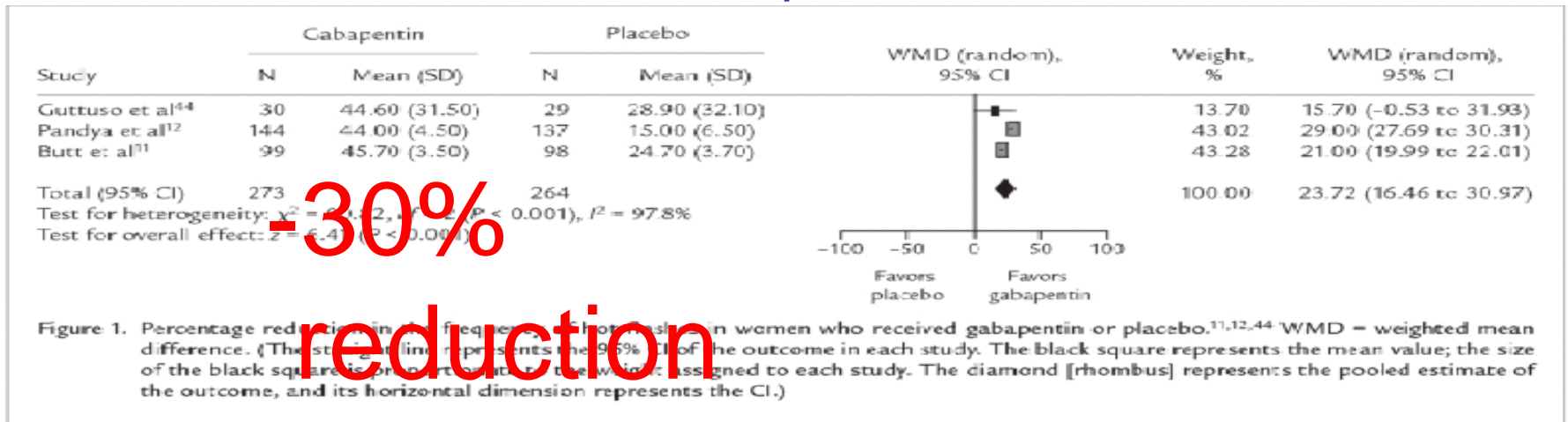


Loprinzi C L et al. JCO 2009;27:2831-2837

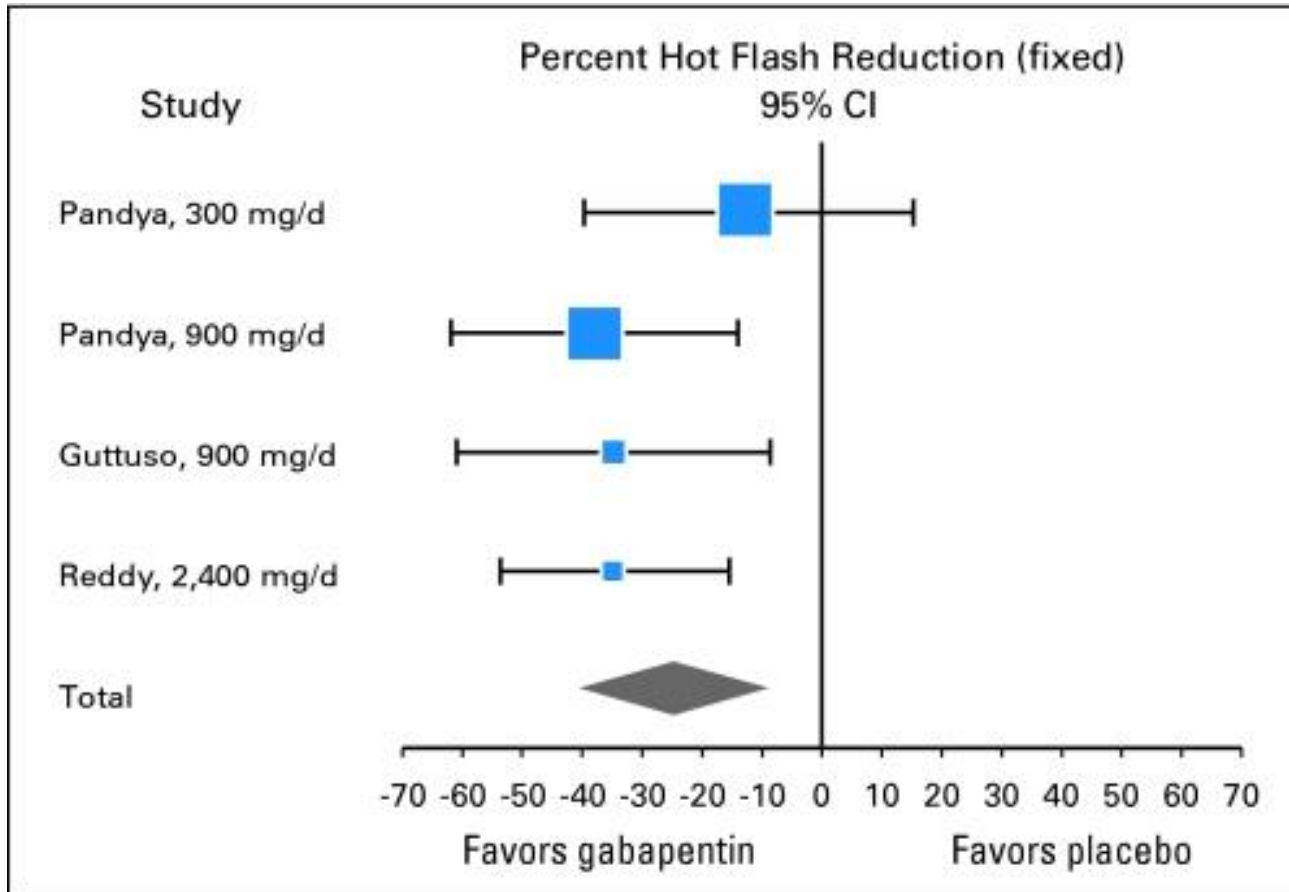
Gabapentin

- GABA analogue used in the treatment of epilepsy, neurogenic pain, restless-leg syndrome, ...

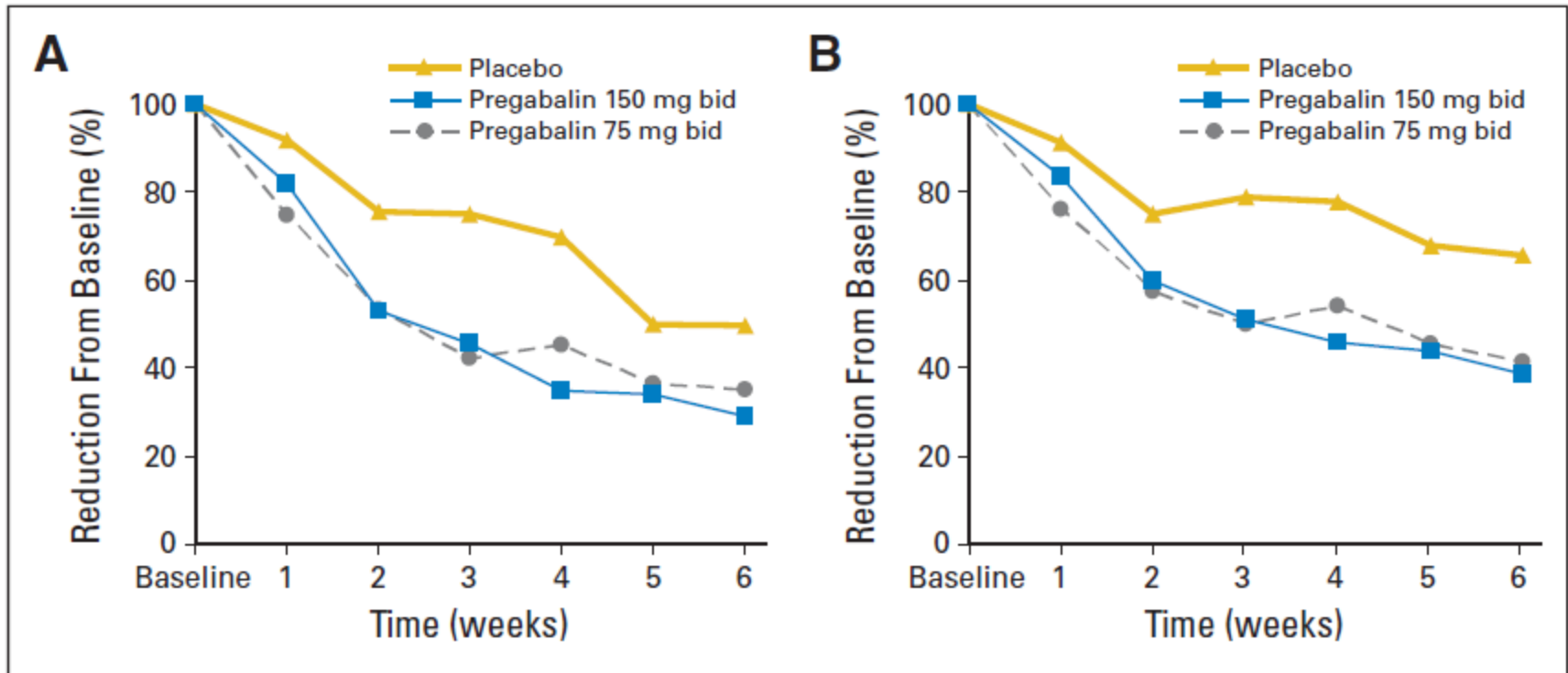
Systematic review & meta-analysis: Gabapentin for hot flashes in women with natural or tamoxifen-induced menopause:



Metaanalysis of gabapentin



Median changes from baseline for (A) hot flash scores and (B) hot flash frequencies for the three study arms. bid, twice per day.

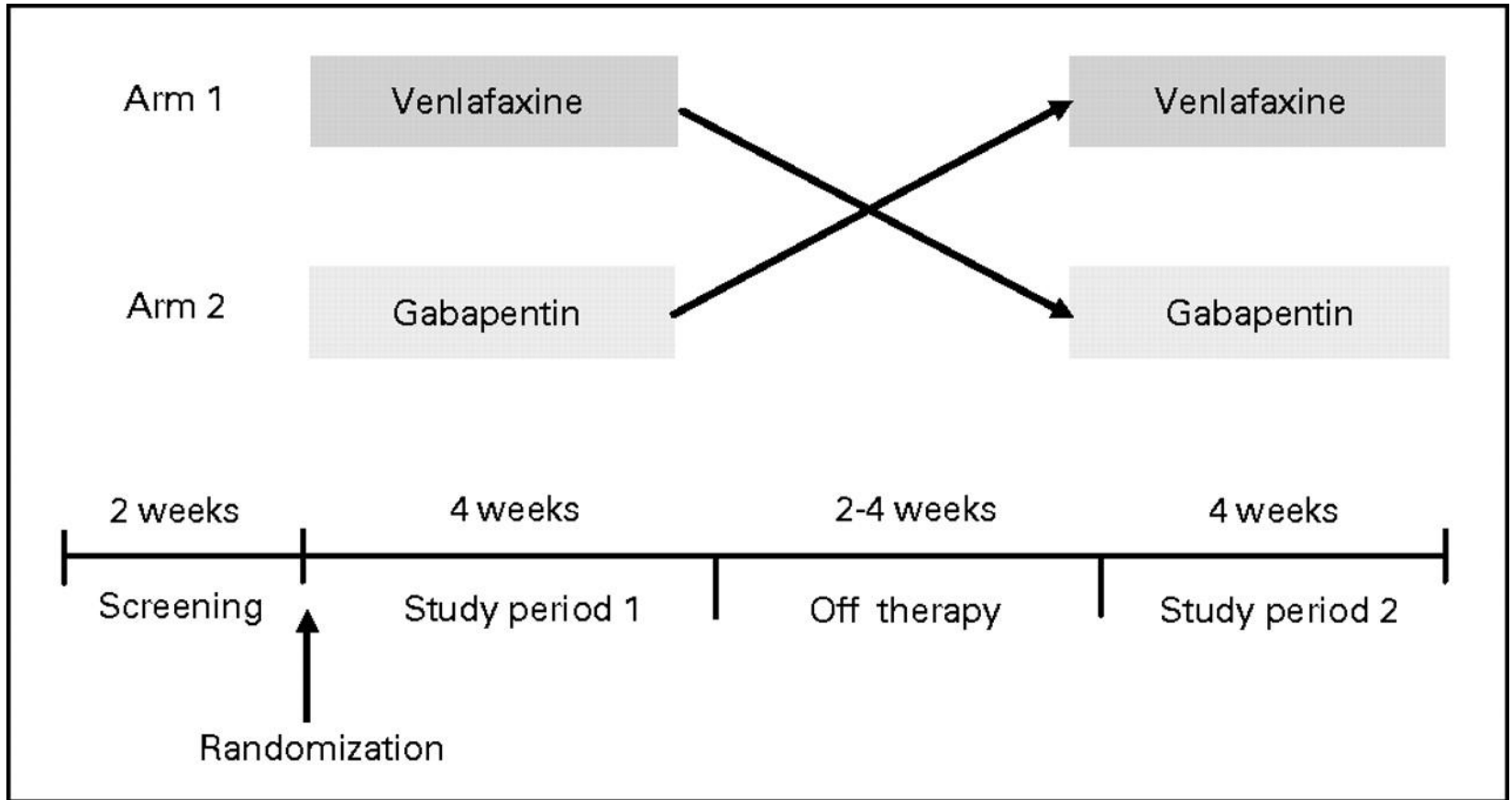


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Multicenter, Randomized, Cross-Over Trial of Venlafaxine vs Gabapentin in Br Ca Survivors

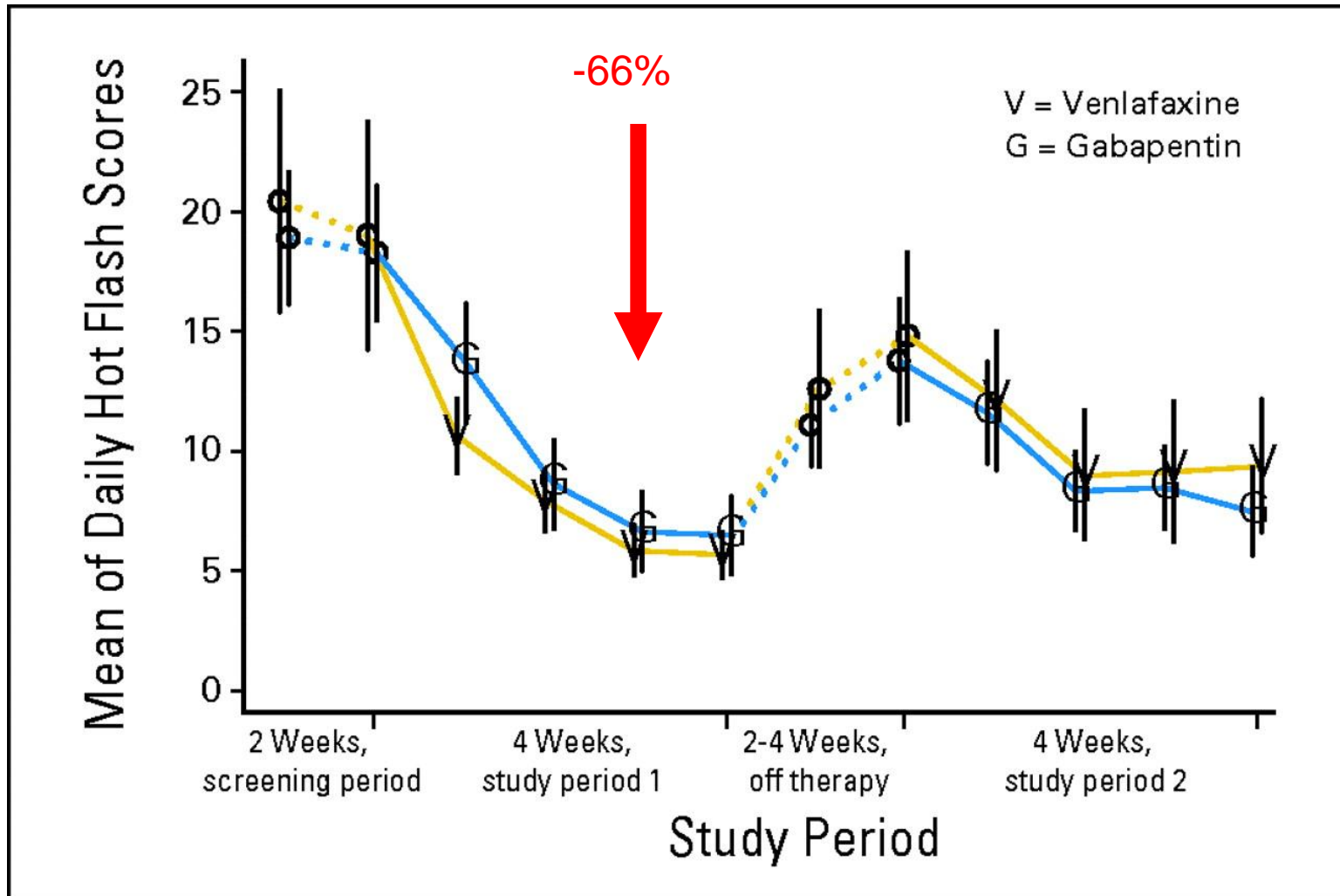
- open-label, randomized, cross-over trial of 4 weeks of venlafaxine (37.5 mg/d (7 d) followed by 75 mg/d (21 d) vs gabapentin (300 mg/d (3 d), then 300 mg X2/d (3 d) then 300 mgX3/d (22 d)
- Patient preference as the primary outcome.
- Postmenopausal women ≥ 14 bothersome hot flashes/week for the prior month.
- A 2-week baseline period and a 2-week tapering/washout time was used before the first and second treatment periods, respectively.
- Bordeleau et al JCO 2010

Study schema.



Bordeleau L et al. JCO 2010;28:5147-5152

Mean daily hot flash scores plotted by study week.



Bordeleau L et al. JCO 2010;28:5147-5152

Table 2. Patient Preference

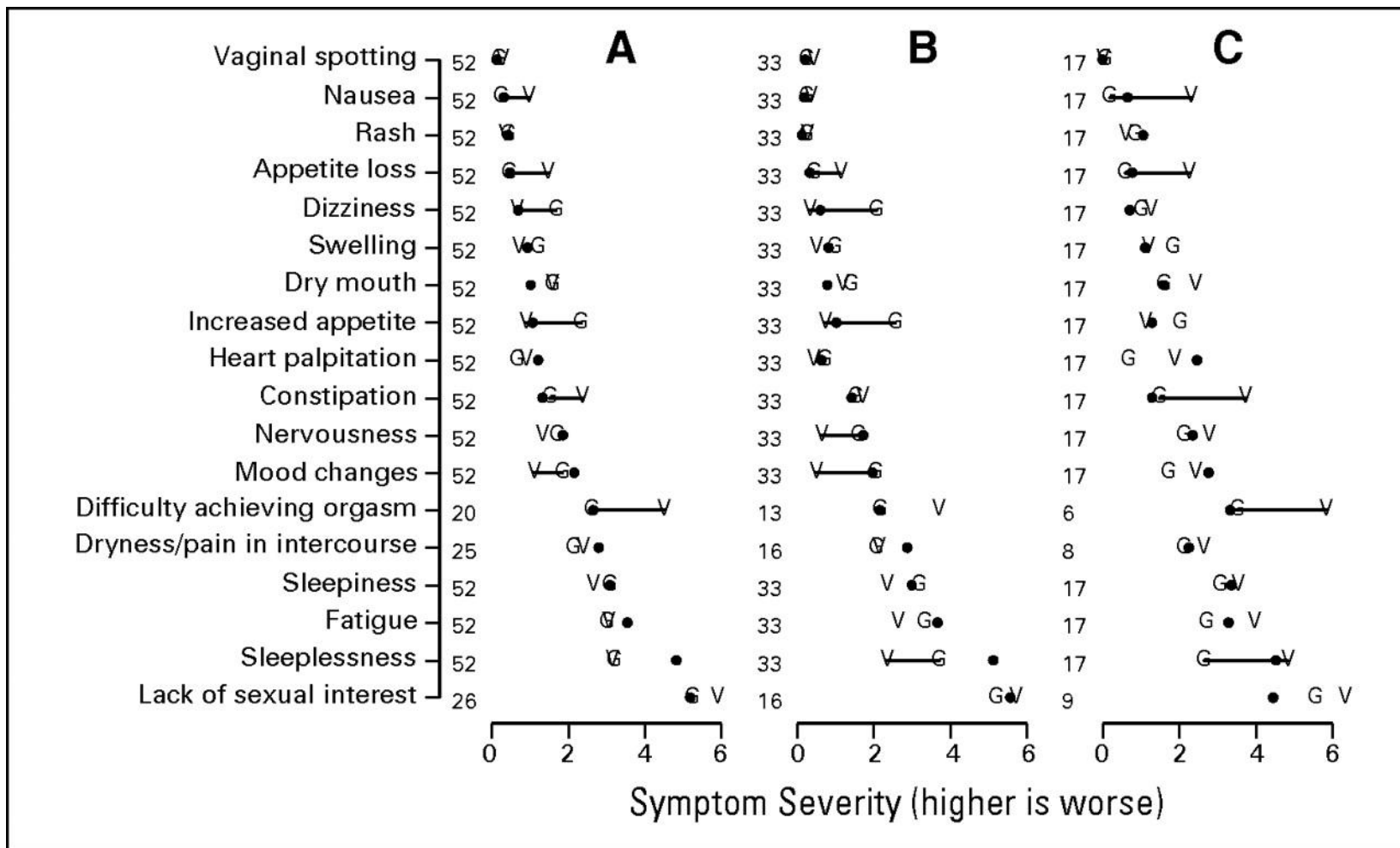
Preference	Prefer Gabapentin (n = 18)		Prefer Venlafaxine (n = 38)		Total (N = 56)	
	No.	%	No.	%	No.	%
How much better was the preferred treatment?						
Much better	12	66.7	22	57.9	34	60.7
A little better	6	33.3	16	42.1	22	39.3
Reasons for preference						
Decreased severity of hot flashes	17	94.4	36	94.7	53	94.6
Decreased frequency of hot flashes	17	94.4	32	84.2	49	87.5
Few adverse effects	11	61.1	22	57.9	33	58.9
Future plans for hot flash treatment						
Would like to continue with preferred drug	10	55.6	29	76.3	39	69.6
Would like to try other drug	3	16.7	2	5.3	5	8.9
Do not want to be on any treatment	3	16.7	7	18.4	10	17.9
Missing	2	11.1	0	0	2	3.6

18

38

56

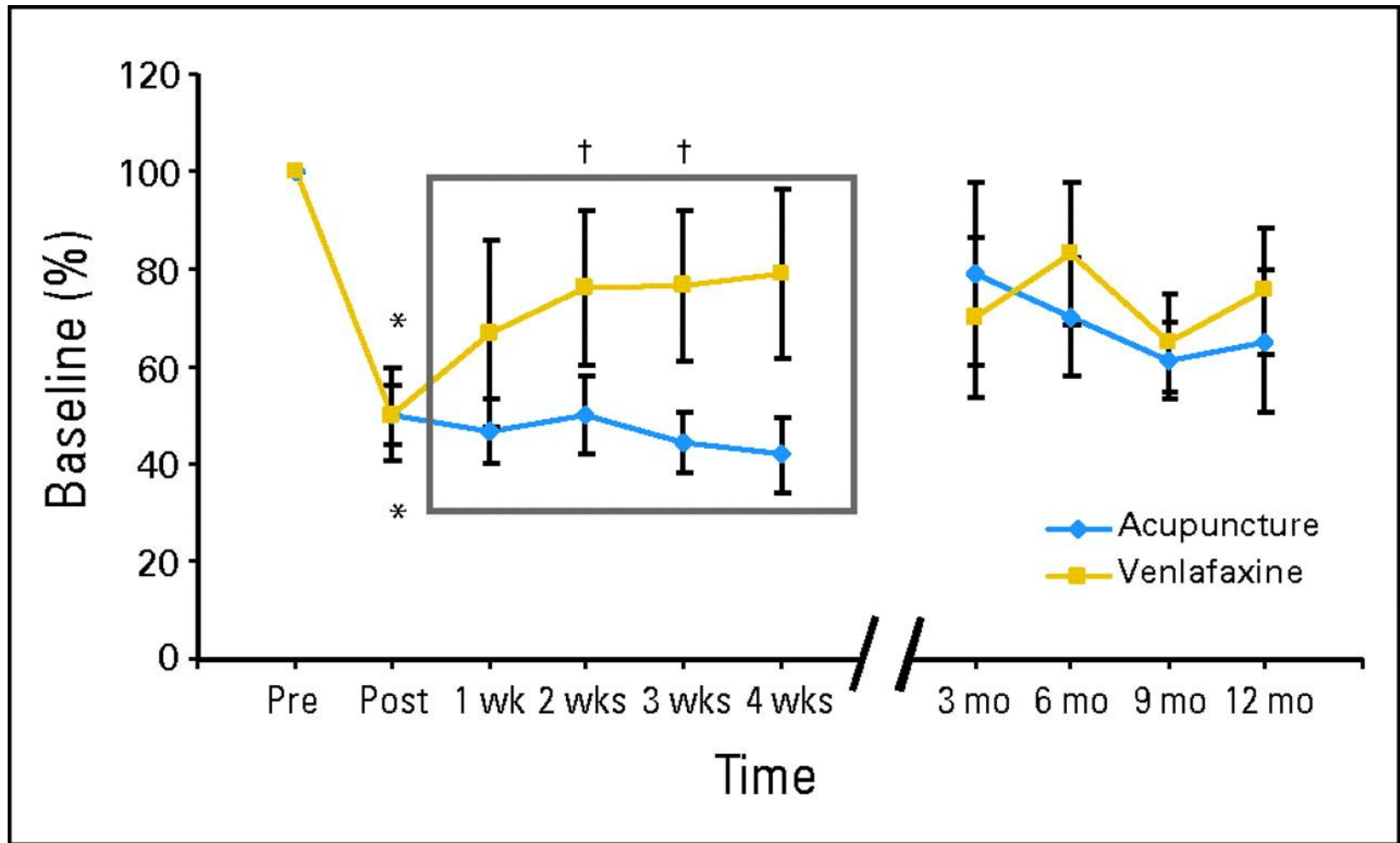
Mean symptom severity at baseline (solid circle) and on treatment with venlafaxine (V) and gabapentin (G) are plotted along the horizontal axis.



Bordeleau L et al. JCO 2010;28:5147-5152

- There is insufficient evidence about efficacy and safety to support the use of alternative medicine in the treatment of menopausal symptoms after breast cancer.

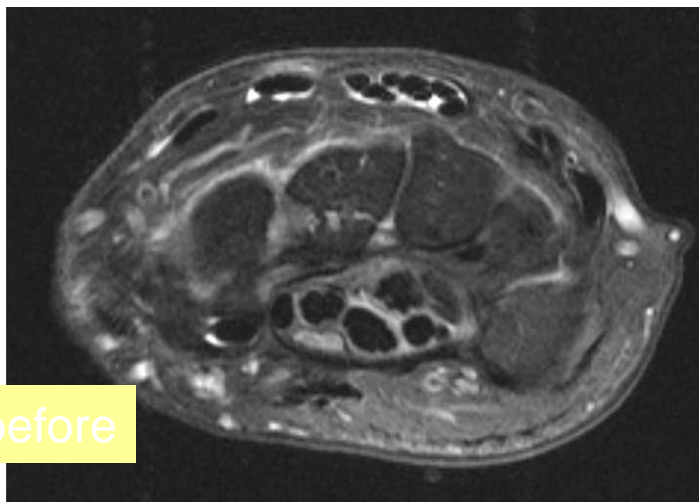
Hot flash frequency (mean \pm SE of the mean) as a percentage of baseline for acupuncture and venlafaxine groups at pretreatment (Pre), post-treatment (Post), and follow-up times of 1, 2, 3, and 4 weeks and 3, 6, 9, and 12 months post-treatment.



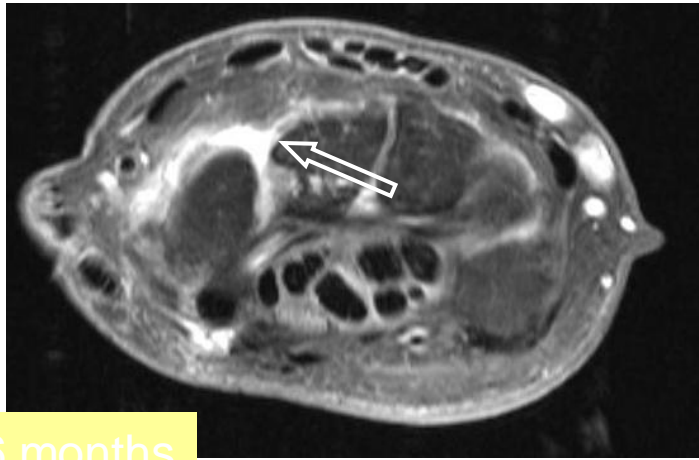
Walker E M et al. JCO 2010;28:634-640

General recommendations

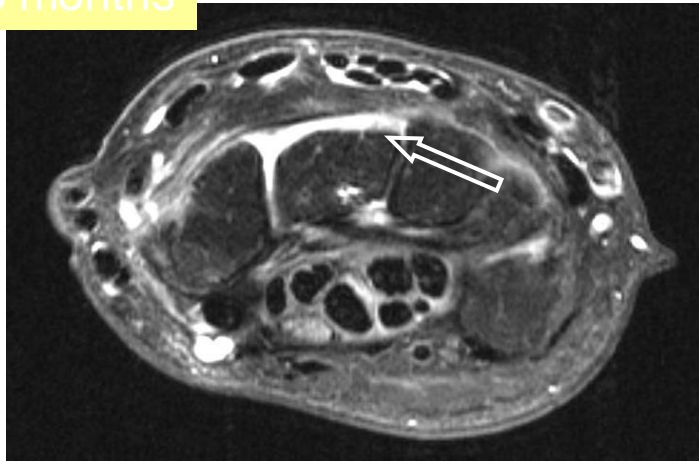
- Achieve a normal weight
- Identify triggers to their hot flashes (eg, alcohol, hot drinks, or spicy food) ?



before



6 months



MRI examination of the wrist on AI showing synovial changes of carpal joint.

Baseline T2-weighted image with fat suppression of the wrist in a transverse plane

There is thickening of synovium of wrist present on the T1- weighted image with fat suppression (open arrow).

The T2-weighted image with fat suppression shows an increase of the amount of intra-articular fluid in wrist (open arrow).

dark circles are the flexor tendons passing through the carpal tunnel

Morales et al JCO V/ 2008

Courtesy of P Neven

AI-induced musculoskeletal syndrome (AIMSS)

- Arthralgia, musculoskeletal pain, carpal tunnel syndrome (CTS), joint stiffness, paresthesia.
- mechanism remains unclear
- Ultrasound/ MRI: fluid in the digital flexor tendon sheath and thickening of the tendon sheath
- Risk factors : Prior use of HT, ER +, obesity, BMI, prior chemo, younger postmenopausal
- surrogate marker of the effectiveness of the hormonal therapy ?
- reversible upon AI withdrawal
- symptomatic treatment: lifestyle -> NSAID, switch to another AI (or tamoxifen), acupuncture, diuretic agent ? testosterone ?

Caution: Vaginal estradiol appears to be contraindicated in postmenopausal women on adjuvant aromatase inhibitors

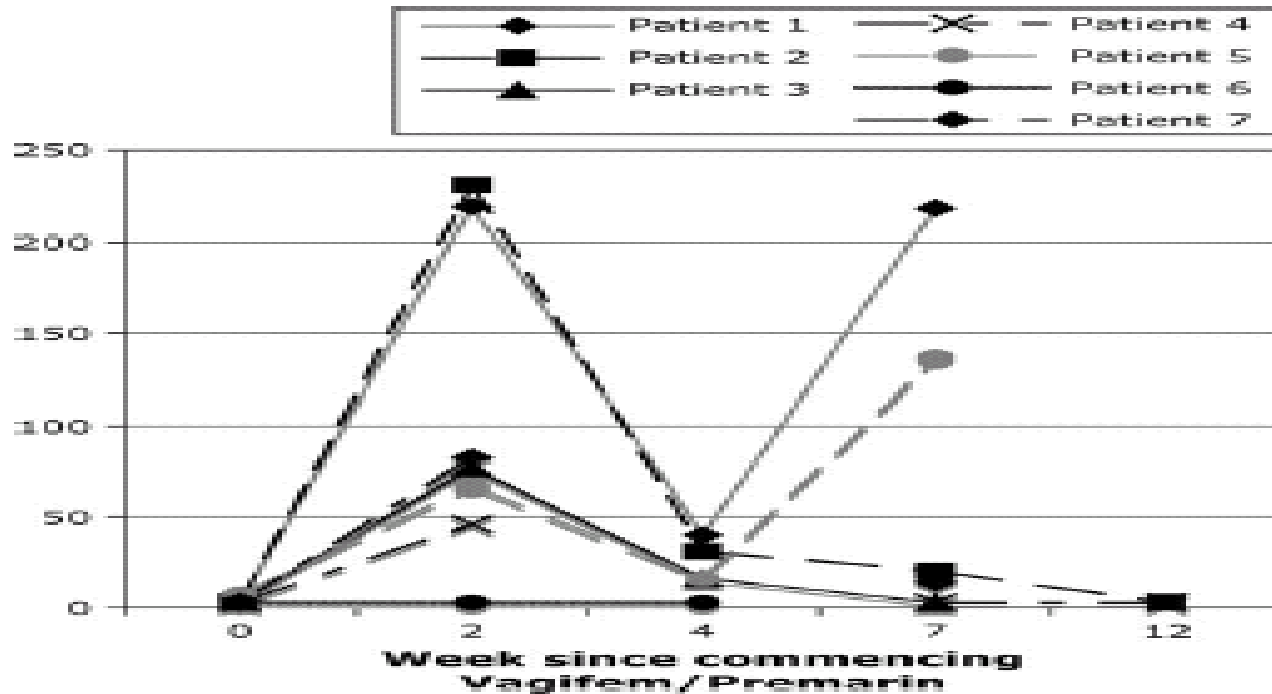
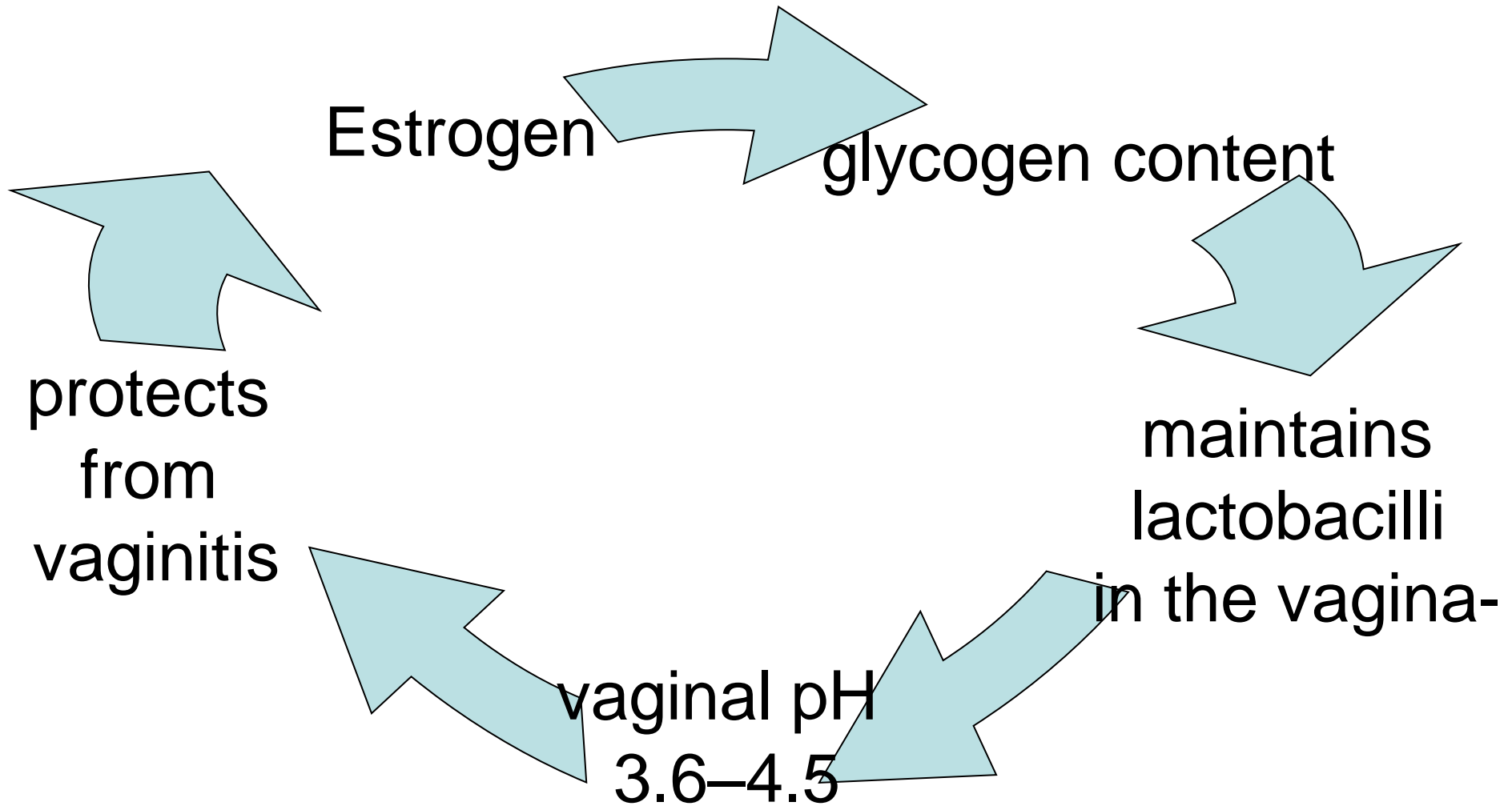


Figure 1. Serum estradiol levels in women receiving concurrent aromatase inhibitors and Vagifem.

Vaginal dryness

- Vaginal E3 lower serum levels than E2
- Lubrifiants
- Vaginal moisturizer (Replens®:non-hormonal polycarbophil-based)
- Oral pilocarpine (non-selective muscarinic receptor agonist of the parasympathetic nervous system).
- Psycho-educational group intervention improving sexual well-being.

Maintaining a low pH in the vagina may reduce the incidence of vaginitis



Atrophic vaginitis

Low Estrogen

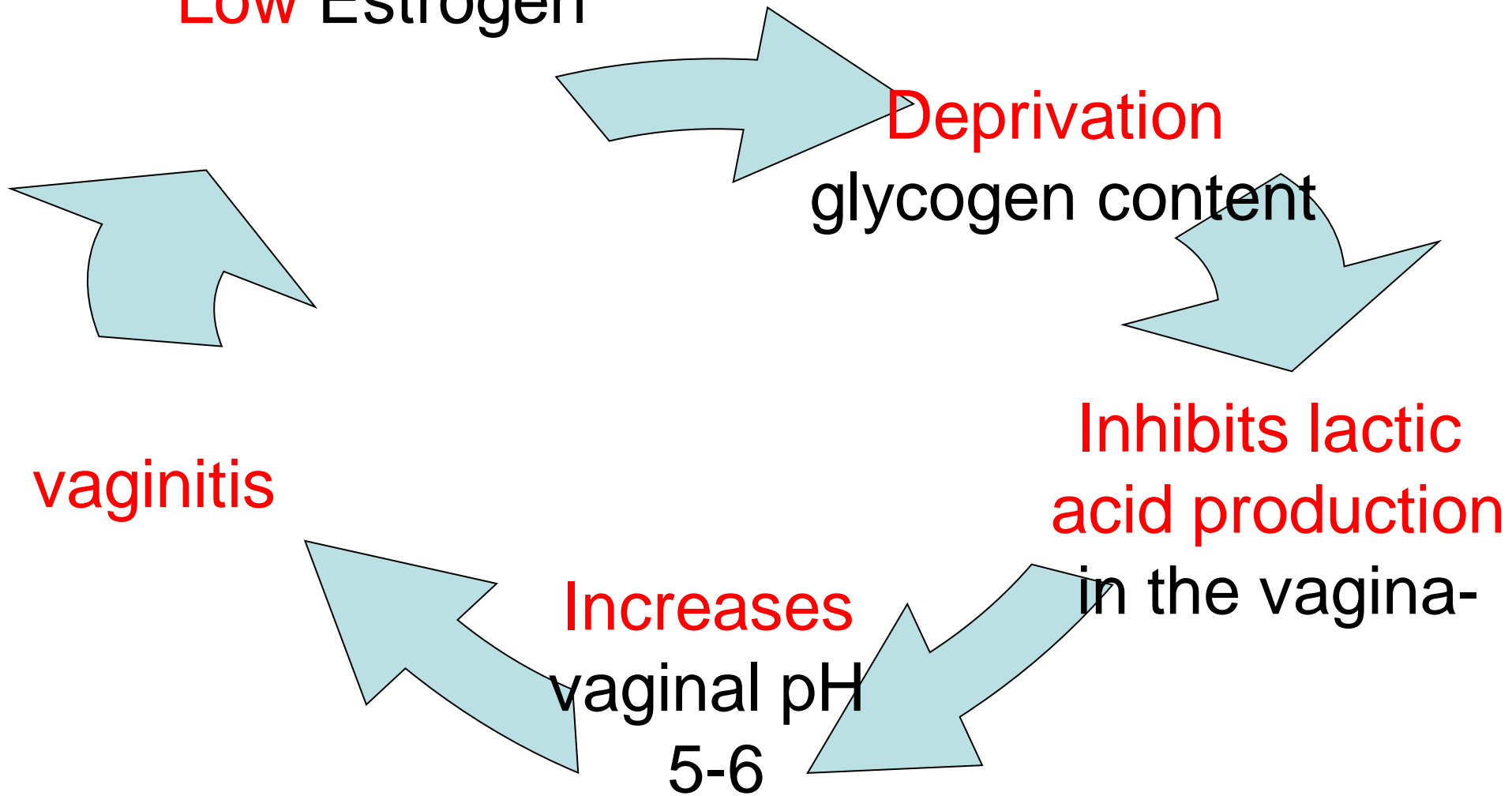
Deprivation

glycogen content

Inhibits lactic acid production
in the vagina-

Increases
vaginal pH
5-6

vaginitis



Vaginal pH-balanced gel for the control of atrophic vaginitis among breast cancer survivors: a randomized controlled trial.

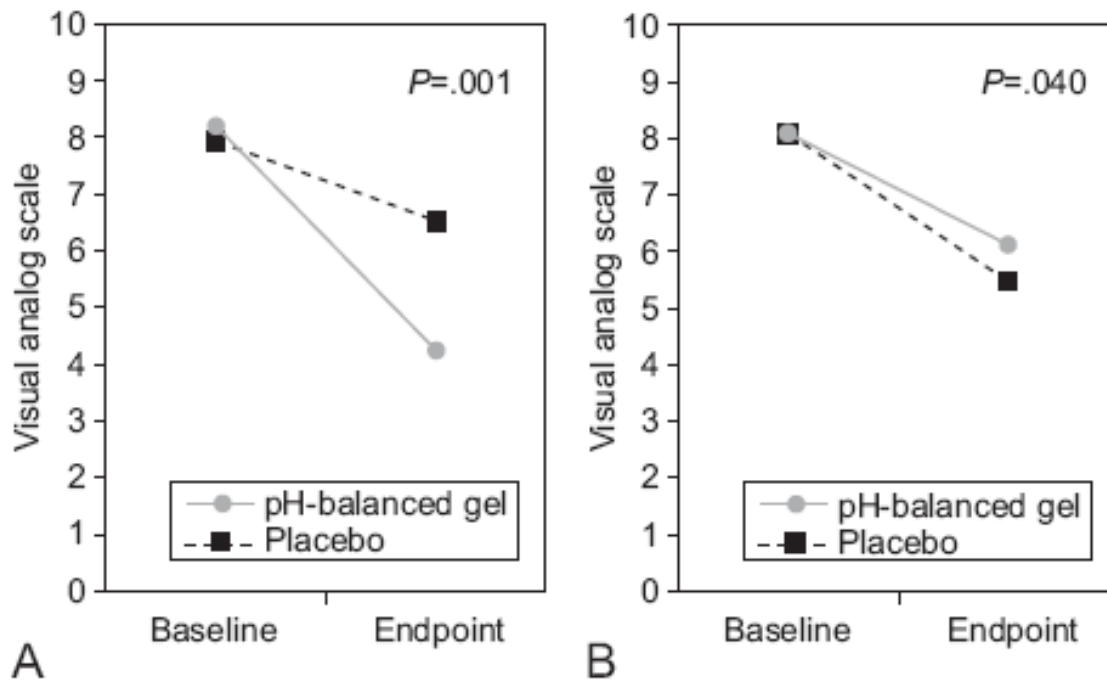


Fig. 2. Changes in the mean visual analog scale (VAS) score 12 weeks after treatment. **A.** Dryness with pain. **B.** Dyspareunia.

Lee. pH-Balanced Gel for Breast Cancer Survivors. Obstet Gynecol 2011.

Conclusions

- Breast cancer patient suffer more often from menopausal symptoms.
- Promote adequate life style.
- Flushes : antidepressants or gabapentin.
- Vaginal dryness : vaginal balanced ph gel or weak estrogens

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