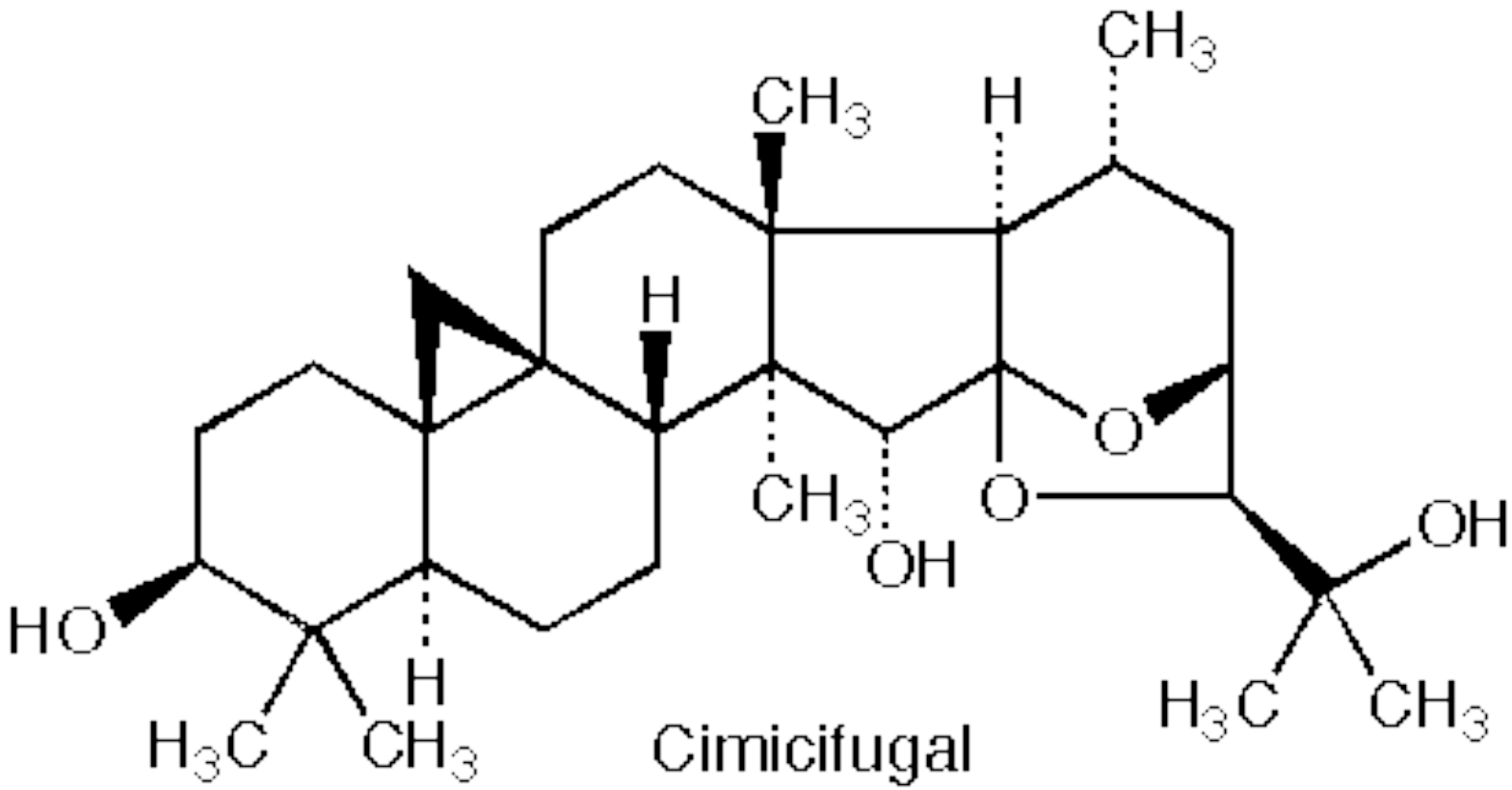
Black Cohosh

- Botany
  - Actaea (Cimicifuga) racemosa. A tall perennial shrub native to Eastern USA; roots and rhizomes used
- History
  - Used by Native Americans for women's health problems and a variety of other uses; A component of Lydia Pinkham's elixir,
  - In Europe a special black cohosh extract (Remifemin) has been used since the 1950s for symptoms of menopause and PMS
- Chemistry
  - Contains phytosterin, salicylic acid, tannins, and triterpine glycosides that may be important for activity
  - The triterpine glycosides include acetin, 27-deoxyacetin, and cimicifugoside



Cimicifugal

Pharmacology

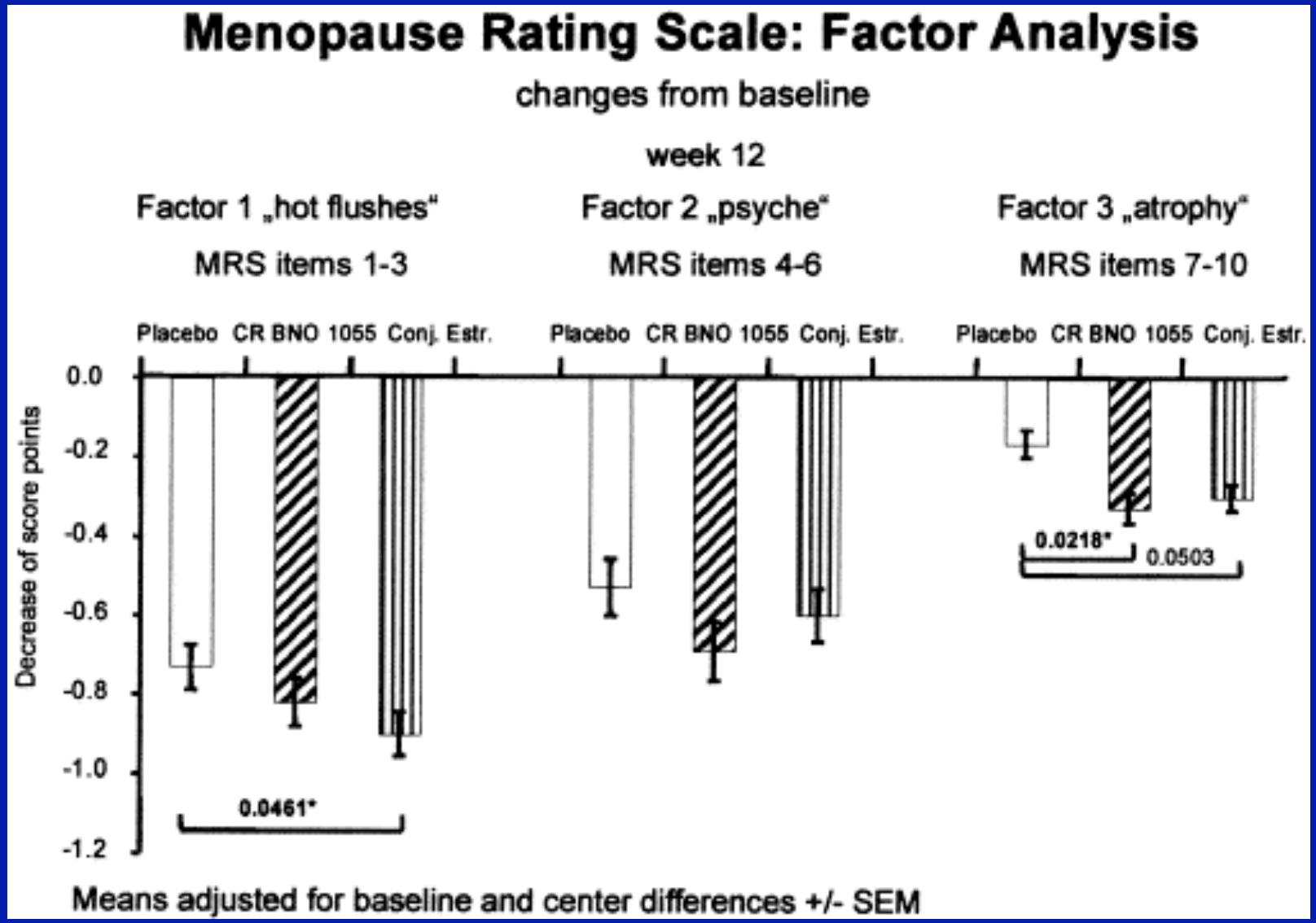
- black cohosh seems to have no effect on uterus or hormone levels(Liske et al. J Women's Health and Gender Based Med. 2002;11:163-174)
- May have central CNS effect on serotonin receptor
- Does not seem to stimulate estrogen receptor dependant tumors in animals or in vitro tumor cell growth. Humans?

Uses

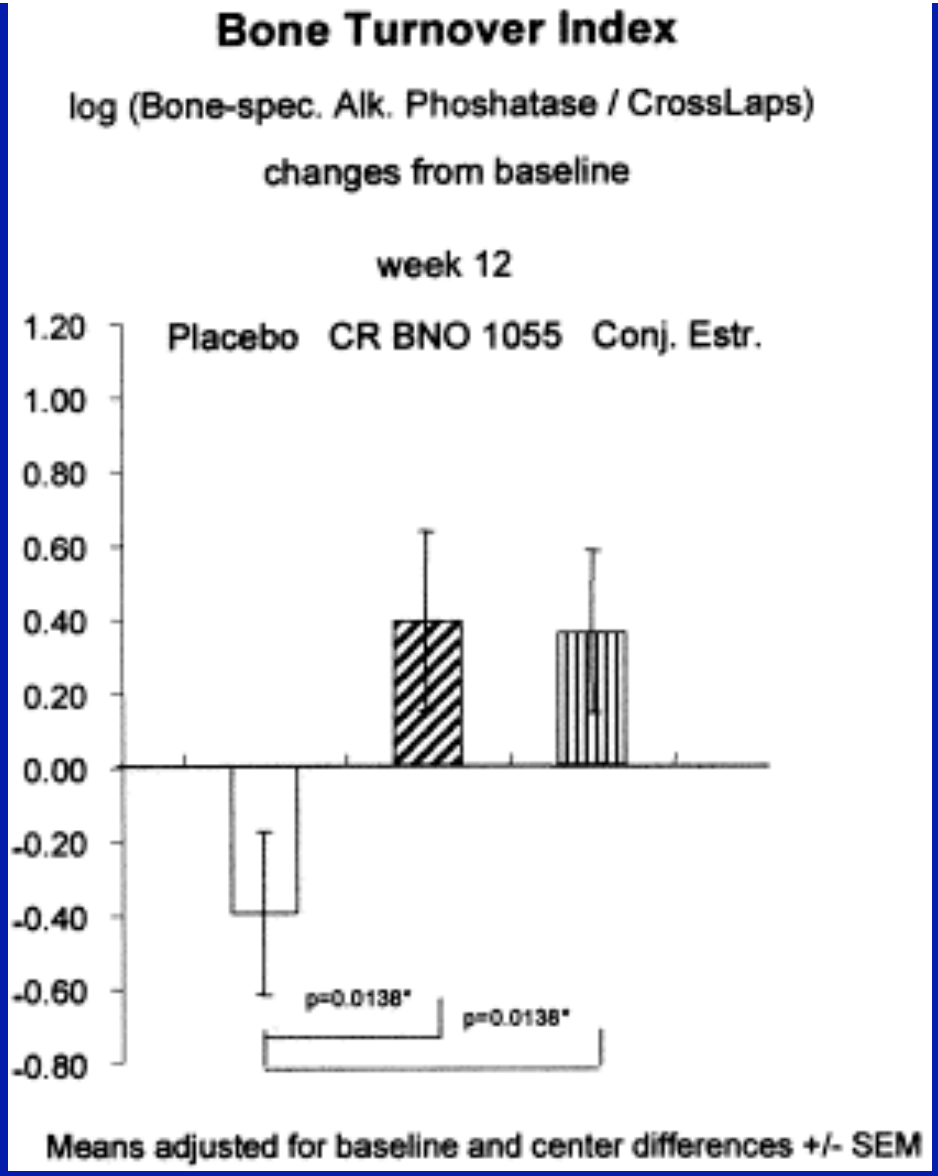
- reduce symptoms associated with menopause
- relieve symptoms of menopause associated with tamoxifen therapy
- PMS
- dysmenorrhea
- hasten childbirthing

•Evidence for relief of menopausal symptoms

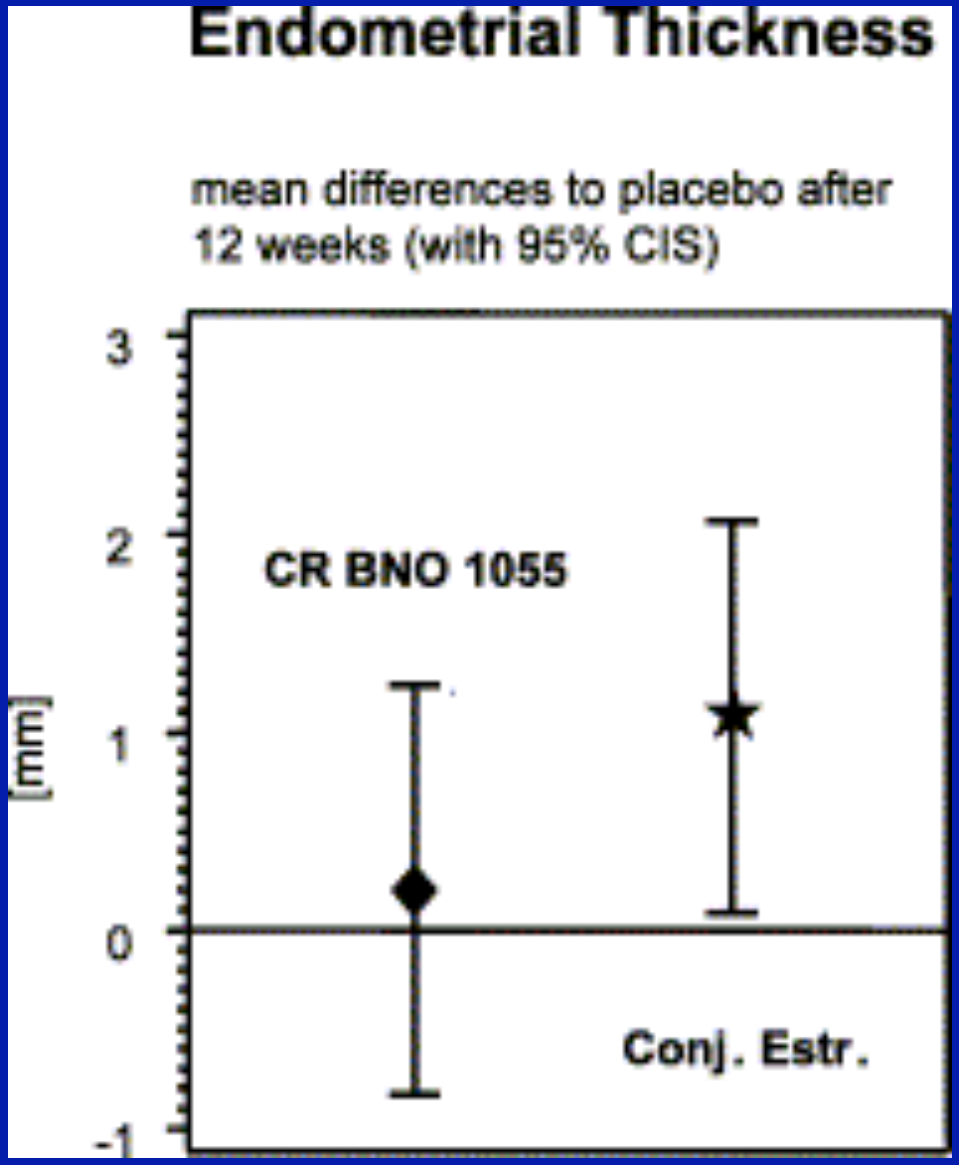
- Early studies with Remifemin show support for reducing hot flashes, etc in menopause
- well designed studies indicate benefit
- However, a recent well designed study done here (see slide) showed no effect but Remifemin was not the product tested



Wuttke et al. Maturitas 2003;44:S67-S77; n=62; 40mg/d for 3 months.



Wuttke et al. Maturitas 2003;44:S67-S77; n=62; 40mg/d for 3 months.



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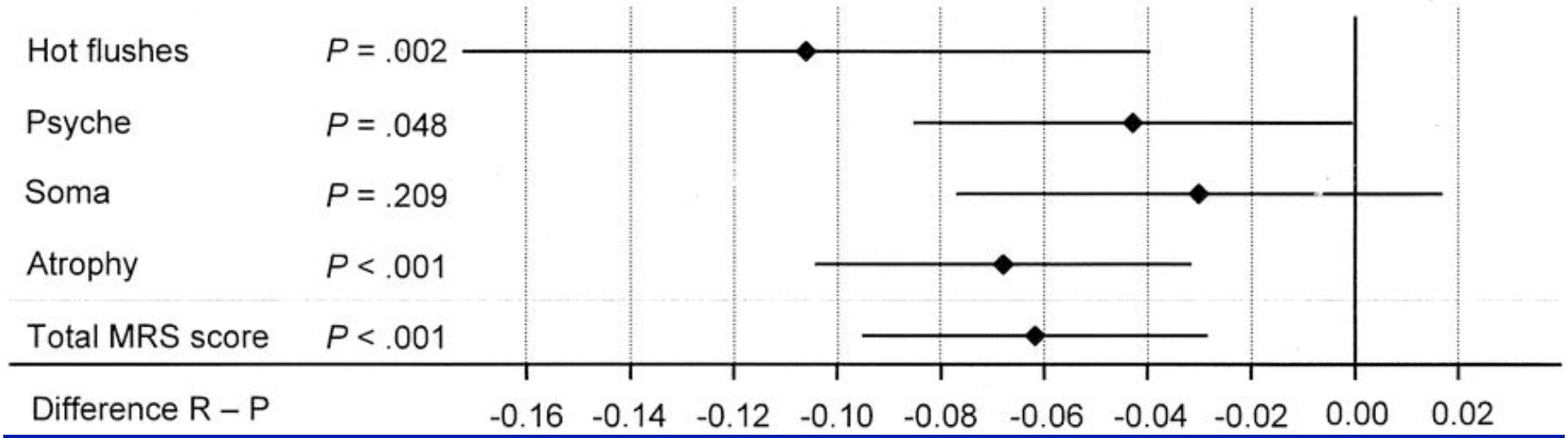
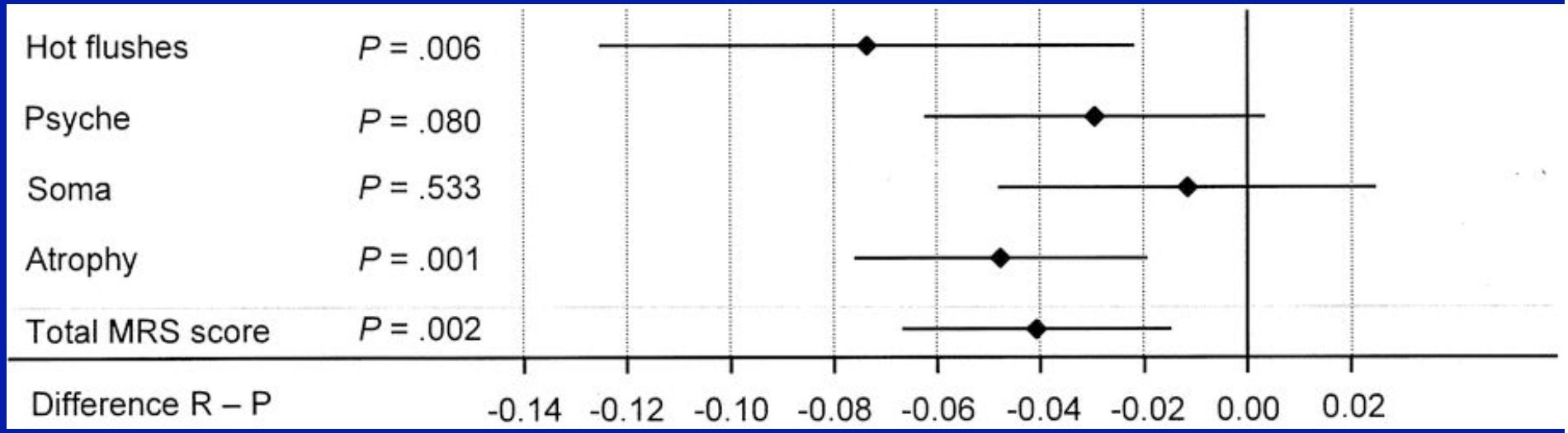


Osmers et al. Obstet Gynecol 2005;105:1074-83. N=304; 40mg extract for 12 weeks. (Remifemin)

Above are results in early climateric women



Osmers et al. Obstet Gynecol 2005;105:1074-83. N=304; 40mg extract for 12 weeks.

Above are results in late climateric women

Nappi et al. Gynecol Endocrinol 2005;20:30-5.
n=64

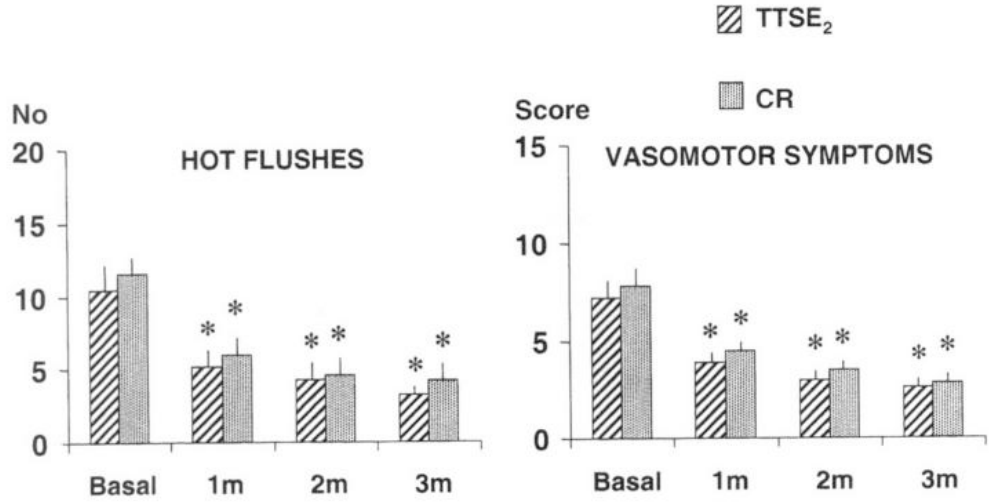


Figure 1. Mean (± standard deviation) number of hot flushes per day recorded in a diary throughout the 3 months of treatment and mean Greene score for vasomotor symptoms recorded monthly in postmenopausal women treated with either *Cimicifuga racemosa* (CR) or low-dose transdermal estradiol ($TTSE_2$). Significance (*) is reported in the text.

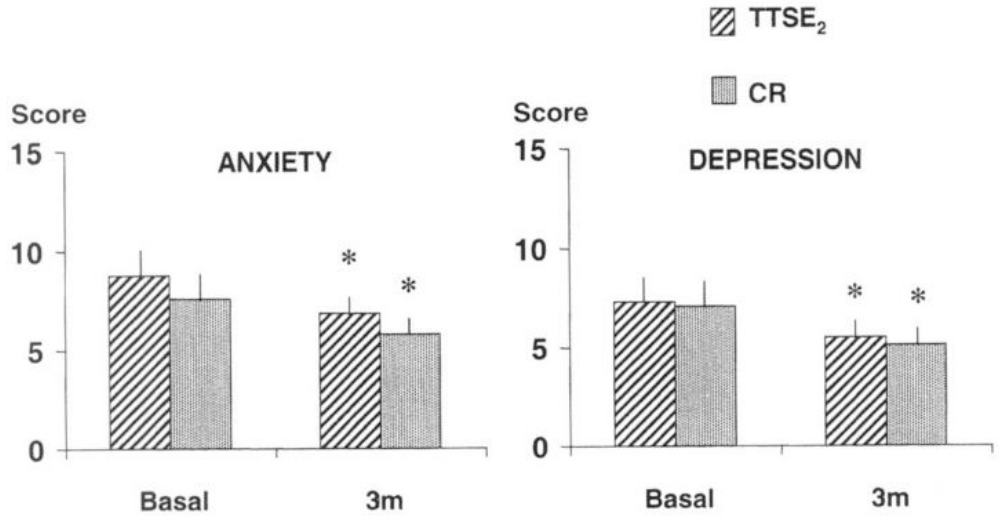
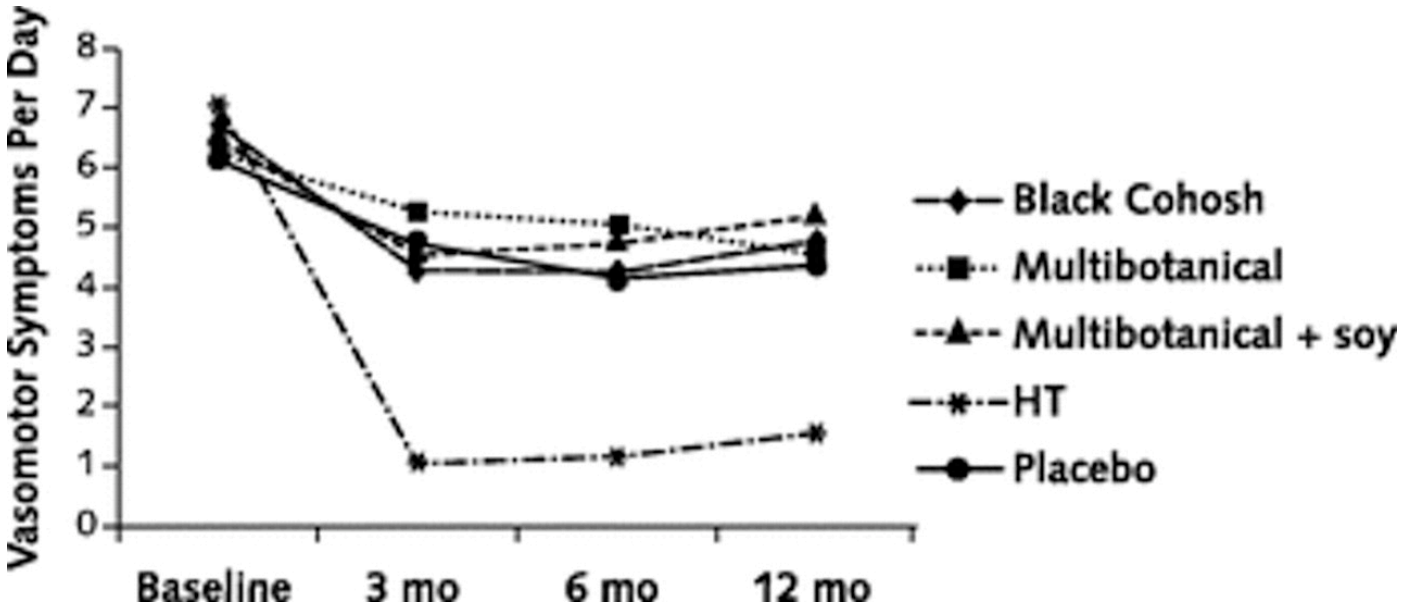


Figure 2. Mean (± standard deviation) Symptom Rating Test score for anxiety and depression recorded before and after 3 months of treatment with either *Cimicifuga racemosa* (CR) or low-dose transdermal estradiol ($TTSE_2$). Significance (*) is reported in the text.

Adjusted mean number of vasomotor symptoms per day, by study group
Newton, K. M. et. al. Ann Intern Med 2006;145:869-879
N=351 for 1 yr



Evidence for help in tamoxifen therapy:

- Results are mixed. One study showed no benefit
  - Jacobson et al. J Clin Oncol 2001;19:2739-2745 n=85; cohosh product NOT DESCRIBED
  - Munoz and Pluchino. Maturitas 2003;44:S59-S65. N=136; cohosh 20mg/d Menofem® for 12 months.
  - Table 4

Table 4
Hot flushes reduction by CR BNO 1055

Hot flushes	Usual-care group[a] ($n = 46$)	Intervention group[b] ($n = 90$)
Severe	34 (73.9%)	22 (24.4%)
Moderate	12 (26.1%)	26 (28.9%)
None	–	42 (46.7%)

[a] Tamoxifen adjuvant therapy.
[b] Combined therapy: tamoxifen + CR BNO 1055.

Munoz and Pluchino Maturitas 2003;44:S59-S65. N=136; 12 mos

Safety

- GI upset, headache, dizziness possible
- due to possible estrogenic effects, use with caution pregnancy
- in vitro does not stimulate breast cancer cells (in contrast to soy isoflavones) but in vivo the risk is uncertain.
- several reports of severe liver toxicity (causal?)

Products

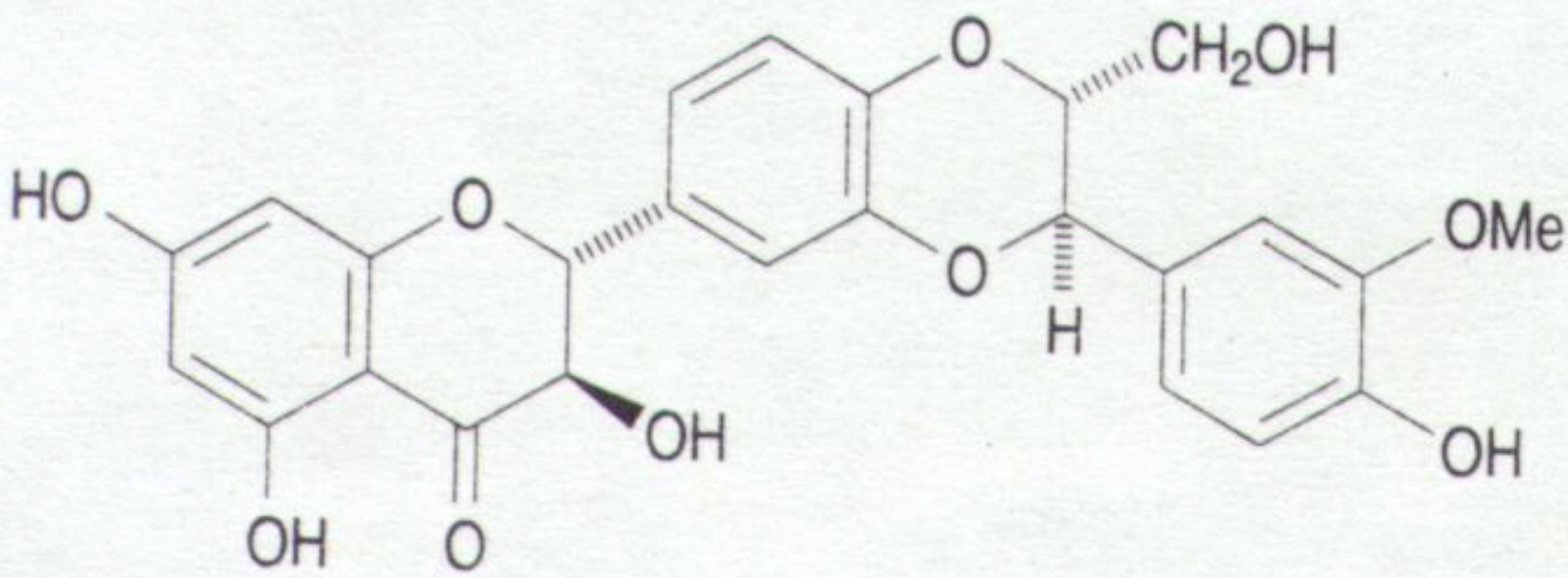
- Remifemin (SK Beecham) is a good product that has been used successfully in controlled trials; it is standardized to contain 1mg of 27-deoxyacetin per 20mg tablet.
- 1 BID

Black Cohosh

- **Summary**
  - **Efficacy: conflicting evidence for benefit for relief of menopausal symptoms using products other than Remifemin. Mixed evidence for relief of tamoxifen adverse effects.**
  - **Safety: good but a few case reports of liver toxicity. Safety in women with existing breast cancer is uncertain.**
  - **Drug interactions: weak 2D6 induction?**
  - **Product selection: standardized root extract; 20mg BID; Remifemin seems to work.**
  - **Questions remaining include**
    - ***What is the risk in breast cancer?***
    - ***What is the risk for hepatotoxicity?***

Milk Thistle

- Botany
  - Silybum marianum
  - Asteraceae family (daisy, thistles, artichoke)
- History
  - long used to treat “liver problems
- Chemistry
  - fruits/seeds contain flavonolignans
  - silymarin=crude mixture of flavonolignans; actually is mixture of several e.g. silybinin
  - Seeds generally used



Silybin

Milk Thistle

- Pharmacology
  - silymarin has strong antioxidant properties
  - has ability to block toxin entry through membranes
  - stimulates liver regeneration; undergoes enterohepatic circulation
  - increases glutathione
  - stimulates ribosomal RNA polymerase
  - has anti-carcinogenic activities in vitro and in animals
- Uses
  - liver cirrhosis
  - hepatitis A,B,C
  - liver toxin poisoning (e.g. Amanita philloides mushroom)

Viral Hepatitis (A or B)

in several studies patients "normalized" hepatic function tests faster in the milk thistle group compared to placebo; shorter hospital stay

Hepatitis C – unknown efficacy; Tanamley et al. (Dig Liver Dis. 2004 Nov;36(11):752-9) were not able to show improvement compared to a multivitamin control at 1 yr (n=141).

A recent crossover study (placebo or milk thistle) for 12 weeks (n=17) showed no benefit (Gordon et al. J Gastroenterol Hepatol 2006;21:275-280).

Toxin and Drug Inducted Hepatitis

both animal and some small patient studies show protective effect of milk thistle or silymarin

.

A meta-analysis (Am J Med 2002;113:506-15) concluded no strong benefit but more studies needed; animal studies indicate considerable promise for beneficial activities

- **Alcohol Related Liver Disease**
  - some improvement in liver function tests compared to placebo in limited studies
  - cirrhosis: Pares et al. J. Hepatol 28:615-621, 1998; no effect on survival or clinical course of alcoholics; n=200; 2yr study
  - cirrhosis: (Ferenci et al. J. Hepatol 9:105-113, 1989 showed 58% 4yr survival in treated vs 39% placebo (p=0.036); 4 yr study
  - Lucena et al. (Int J Clin Pharmacol 2002;40:2-8) showed increase in glutathione and decreased liver peroxidation in patients with alcoholic cirrhosis but no change in routine liver tests in treated compared to placebo. N=60
  - Alcoholic cirrhotic diabetics. Velussi et al. 1997;26:871-879. N=60. Open label. Improved

Rambaldi et al. Cochrane Database Syst Rev 2005;2:CD003620. For alcoholic and/or hepatitis B or C liver disease, there were trends for benefit on overall mortality and complications and a statistical reduction in liver-related mortality in all trials (RR 0.5, CI 0.29-0.88) but not in high quality trials (RR 0.57, CI 0.28-1.19). “high quality trials are needed”

Milk Thistle

- Cautions
  - Nothing special
- Interactions
  - None of significance reported as yet. Recently shown to not affect indinavir pharmacokinetics or CYP3A4 or P-glycoprotein.
- Products
  - flavonolignans are not water soluble
  - extract used
  - extracts containing at least 70% silymarin are best
  - A lipid complex of silibin has high bioavailability

New Potential Use in Diabetics

randomized, double –blind, placebo controlled trial (n=51) gave milk thistle extract or placebo for 4 months to diabetics. Glycosylated hemoglobin (HbA1c) and lipid profiles improved.

Huseini et al. Phytother Res 2006;20:1036-1039.

Milk Thistle

Summary

- **Efficacy: possibly helpful for liver injury due to hepatitis and drugs and alcohol but evidence is weak. Some promise for diabetics**
- **Safety: good**
- **Drug interactions: none noted so far. None of significance reported as yet.**
- **Product selection: extract containing 80% silymarin is best**
- **Dose: 200mg TID**
- **Questions remaining include**
  - ***Does milk thistle really work for its hepatitis B or C and for alcoholic liver disease? Will it be useful for diabetic patients?***

Ginseng

- Botany
  - Panax ginseng (Korean or Asian ginseng),
  - Panax quinquefolius (American ginseng)
  - note: Siberian ginseng is different (Eleutherococcus senticosus)
  - steamed and dried product is “red” ginseng vs “white” ginseng which is dried only
- History
- Chemistry-ginsenosides, a series of steroid glycosides. The ratio of these differ between Panax sp.

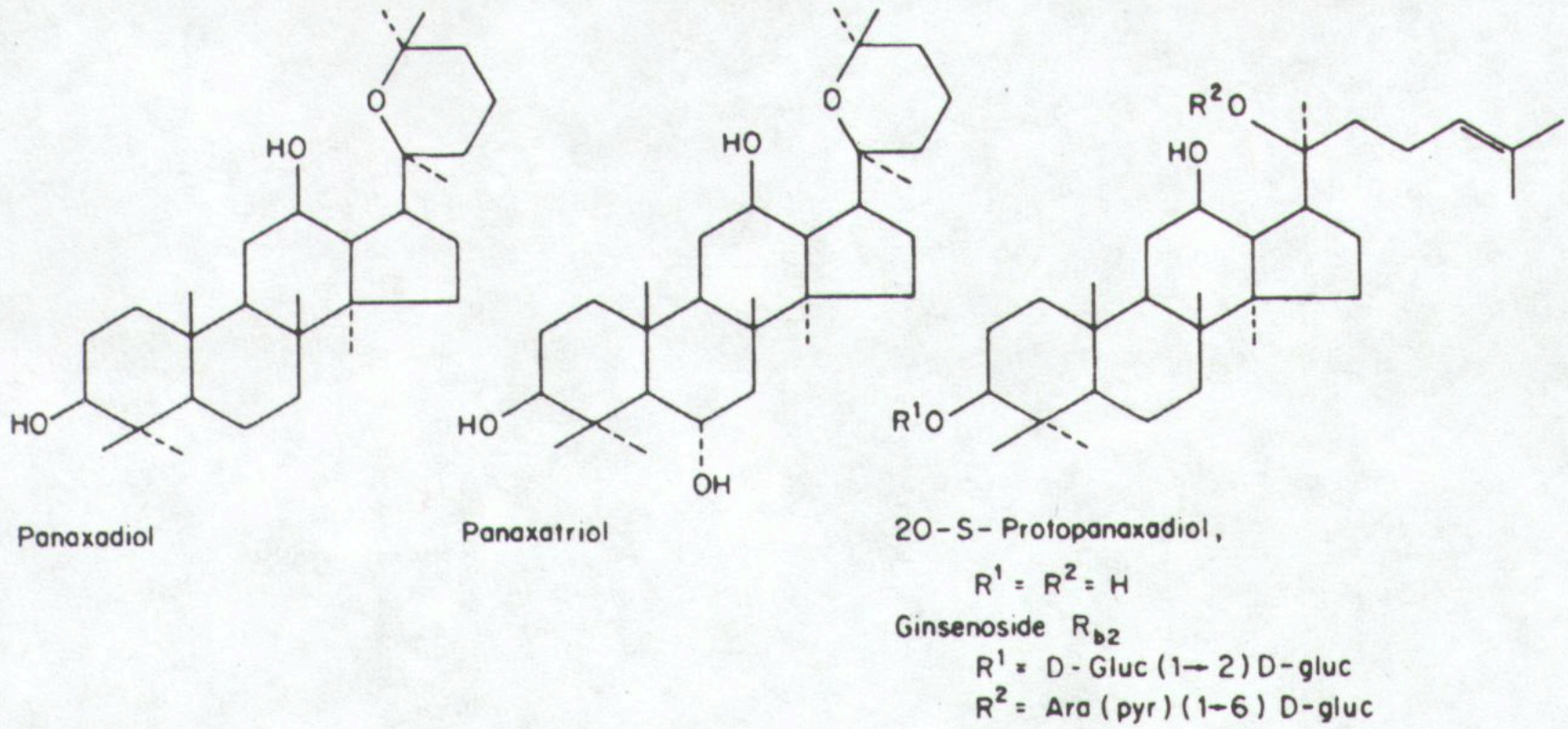


Fig. 22.10. Steroids associated with ginseng.

•Pharmacology – "adaptogen" is the term that perhaps best describes what ginseng is supposed to accomplish.

•Uses

•immune stimulant - animal and human studies (with flu vaccine) indicate that it may enhance the immune response

•sports performance - mixed results but generally negative

•mental functioning – mixed results but some intriguing results indicate promise for enhancing completion of mental tasks and (in combination with ginkgo) memory

•"improved quality of life" – results of small studies are inconsistent

•cancer prevention - one controversial study in Korea showed preventative effects

•hypoglycemic effects in diabetic patients (e.g. Vuksan et al., Diabetes Care 23:1221-1226,2000, Vuksan et al. Nutr Metab Cardiovasc Dis. 2008;18:46-56.) with use of American ginseng and Panax ginseng (Reay et al. J Psychopharmacol. 2006;20:771-81

•Korean red ginseng in one recent study showed to be helpful in erectile dysfunction

•Common cold. Several studies indicatethat a special extract (Cold-FX) showes preventative and treatment benefits

Predy et al. CMAJ 2005;173:1043-1048

Note: special extract of ginseng used that contains polyfuranosyl-pyranosyl-saccharides. Product (Cold-FX) available in Canada and USA. An earlier, smaller study showed activity in preventing flu in older adults (McElhaney et al. *Am GeriatrSoc.* 2004;52:13-19.)

Table 2: Number of colds over the 4-month intervention period*

Outcome	Group; no. (%)† Placebo *n = 149*	Ginseng extract *n = 130*	Difference (95% CI)
Jackson+ colds‡			
No. per person, mean (SD)	0.93 (0.91)	0.68 (0.82)	0.25 (0.04 to 0.45)
1 cold	95 (63.8)	71 (54.6)	9.1 (-2.4 to 20.7)
≥ 2 colds	34 (22.8)	13 (10.0)	12.8 (4.3 to 21.3)
Colds§			
No. per person, mean (SD)	0.99 (1.00)	0.71 (0.83)	0.29 (0.07 to 0.50)
1 cold	96 (64.4)	73 (56.2)	8.3 (-3.2 to 19.8)
≥ 2 colds	37 (24.8)	13 (10.0)	14.8 (6.2 to 23.5)

Note: SD = standard deviation, CI = confidence interval.
*Unless stated otherwise.
†Subjects providing baseline data only (placebo *n* = 21, ginseng extract *n* = 23) were excluded from the data analysis.
‡Total symptom score over 2 days > 14.
§Daily total symptom score > 4.

Table 3: Severity, number of days of symptoms and duration of all colds* over the 4-month intervention period per subject reporting cold symptoms

Outcome	Group; mean (SD) Placebo *n = 96*	Ginseng extract *n = 73*	Difference† (95% CI)
Total symptom score	112.3 (102.5)	77.5 (84.6)	1.5 (1.2-2.0)
Total symptom score per cold	75.9 (68.3)	64.2 (75.1)	1.3 (1.1-1.6)
Total days with cold symptoms, no.	16.5 (13.8)	10.8 (9.7)	1.6 (1.3-2.0)
Duration of each cold, d	11.1 (8.1)	8.7 (7.2)	1.3 (1.0-1.7)

Note: SD = standard deviation, CI = confidence interval.
*Daily total symptom score > 4.
†Statistical analyses were performed on the log-transformed data; differences and confidence intervals were obtained by transforming back to the original scale using antilogs.

- Dose
  - 1-2g/d of dried root
  - 200mg/d of a standardized extract of the root containing 4-7% ginsenosides; it is recommended to take for 4 weeks then stop for 1-2 weeks.
- Adverse Effects
  - much listed but close evaluation indicates wide safety; reports of problems may be associated with poor products and adulterated products
- Drug Interactions
  - may be CYP inducer (more later)

- Bottom Line
  - pick a good product
  - maybe useful in diabetes and in geriatric populations
  - watch for drug interactions with narrow therapeutic index drugs

Ginseng

Efficacy: huge literature of small, uncontrolled studies; some evidence for applications in geriatric patients (improved "quality of life") and in diabetes and common cold and flu (Cold-FX)

Safety: good; reported problems may be due to poor quality product

Drug interactions: may precipitate hypoglycemia with insulin or oral hypoglycemics

Product selection: product should be standardized to deliver about 25mg/dose ginsenosides or about 50mg/d

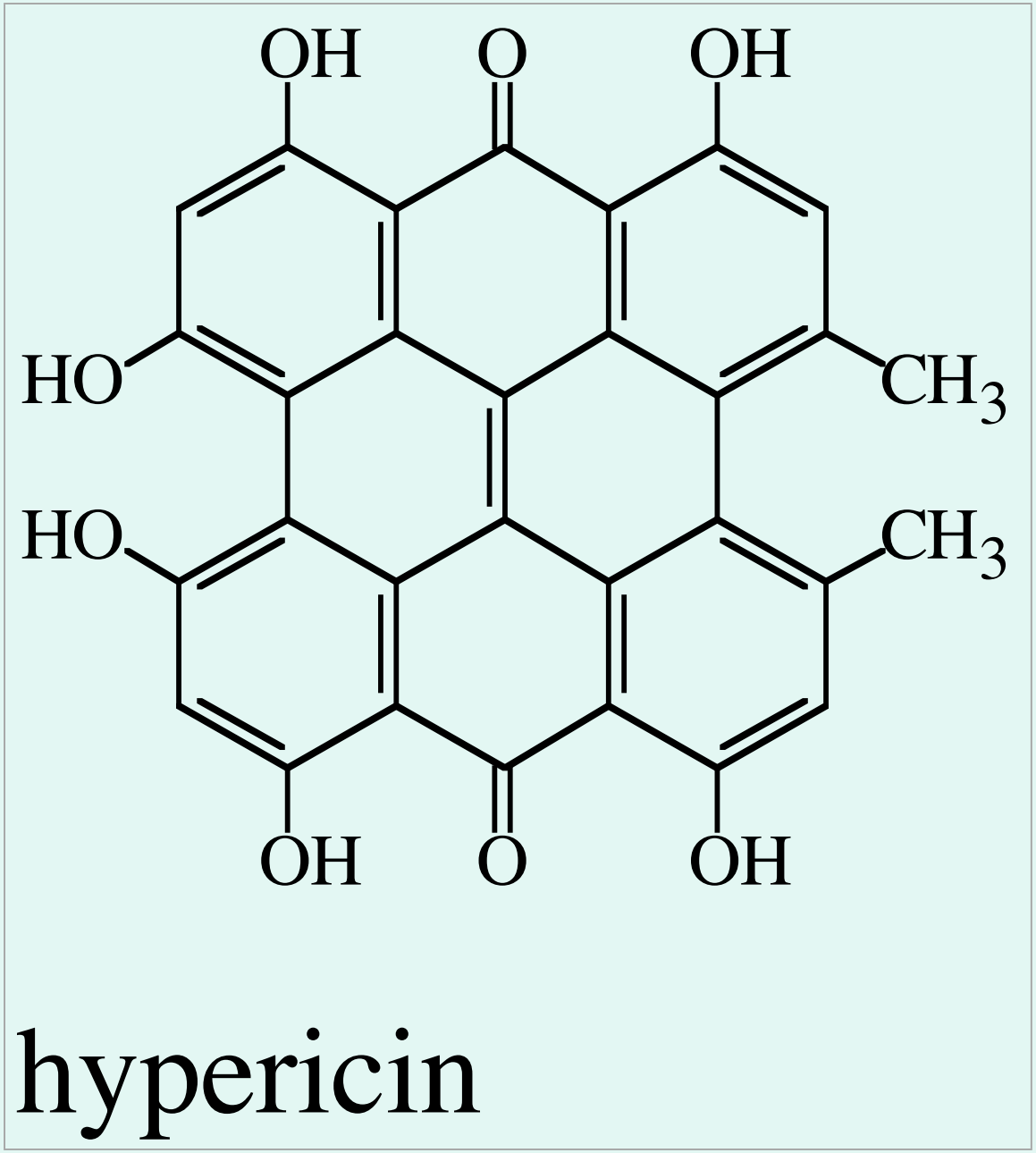
Dose: 200mg per day of extract

Questions remaining include:

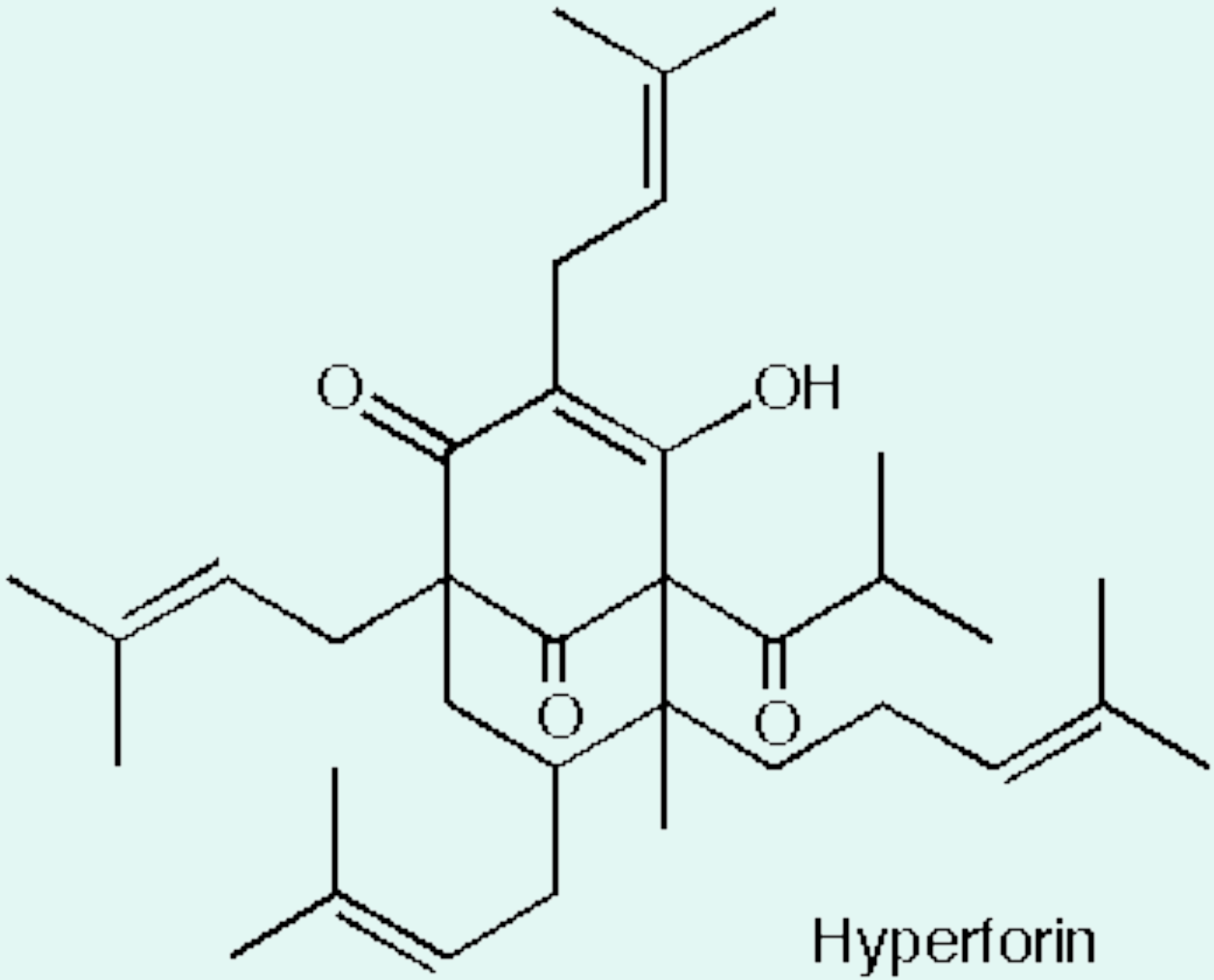
- ***What, actually is this stuff good for!***

St. John's Wort

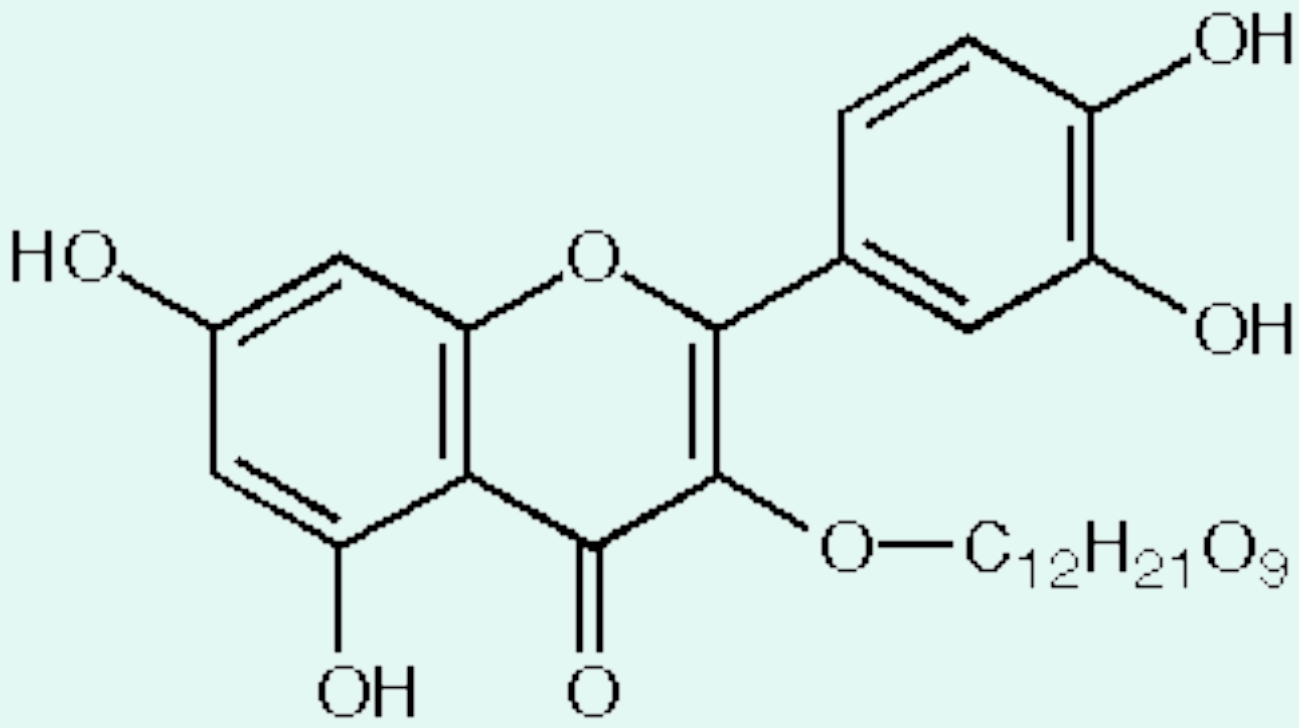
- Botany
  - Hypericum perforatum
- History
- Chemistry
  - Hypericin
  - hyperforin



hypericin



Hyperforin



Rutin
(flavonoid glycoside)

St. John's Wort

- Pharmacology
  - hypericin
    - antiviral acitivity
    - MAOI ? 1984 study found activity but 3 more recent studies say no
  - hyperforin

    more important
  - Flavonoids
    - antioxidant
    - MAOI ? But maybe not in vivo
  - Other? MAOI, SSRI

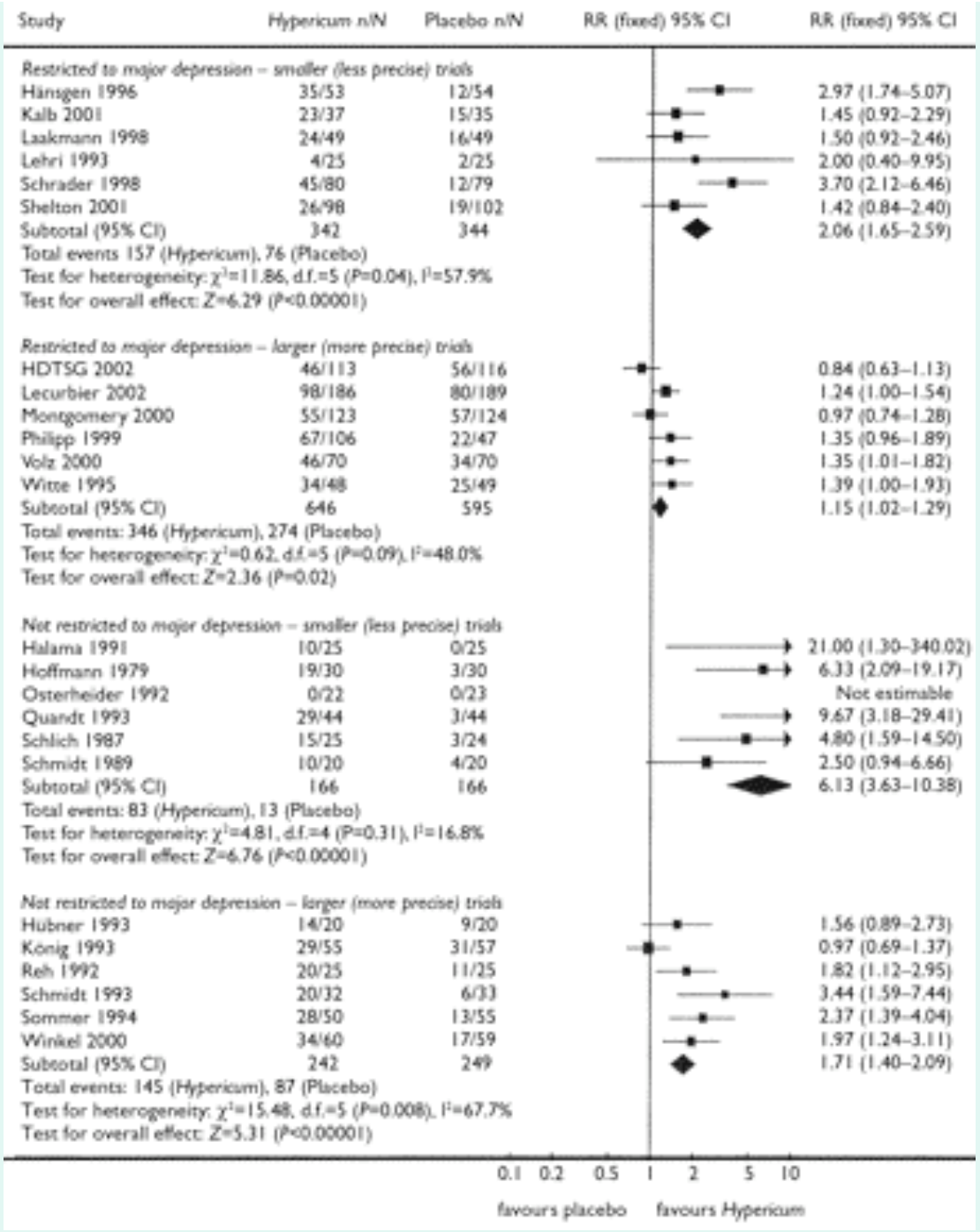
St. John's Wort

- Evidence -Depression
  - widely prescribed in Europe for depression
  - Commission E "approved" for this use
    - Commission E- psychological disturbances, depression, anxiety,nervous unrest; topically the oil for bruises,myalgi, burns

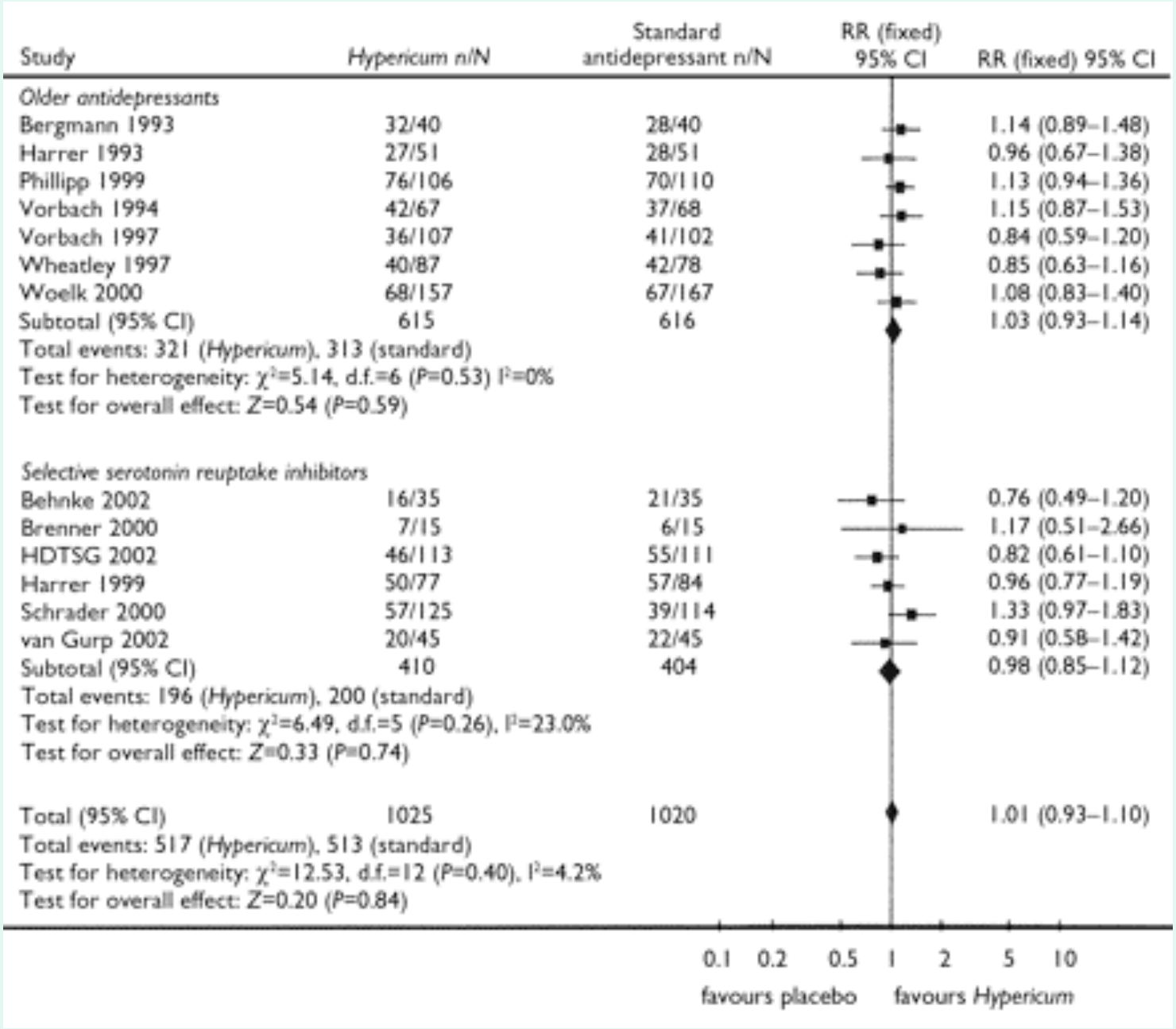
St. John's Wort

- Meta -analysis of 40 randomized trials (Linde et al. Br J Psychiatry. 2005;186:99-107)
  - 26 trials =double blind, placebo controlled; 3320 patients
  - 14 trials = double blind, compared to standard treatment; 2283 patients

Linde et al. Br J Psychiatry. 2005 Feb;186:99-107



Linde et al. Br J Psychiatry. 2005 Feb;186:99-107



St. John's Wort

- **Linde et al conclusions: more effective than placebo, similar to standard drugs but not for major depression**

- **Woelk et al. BMJ 321:536-539, 2000. SJW same as imipramine with fewer adverse effects in multicentered German study (n=324) in patients with mild to moderate depression**

- **Brenner et al. Clin Ther 22:411-419, 2000. SJW same as sertraline in double blind, randomized study (n=30) with mild to moderate depression**

- **Schrader et al. Int Clin Psychopharmacol 15:61-68,2000. SJW same as fluoxetine with fewer adverse effects in multicentered German study (n=240) in patients with mild to moderate depression**

- **Szegedi, A et al. BMJ 2005;330:503. SJW same as paroxitine with fewer adverse events. N=244**

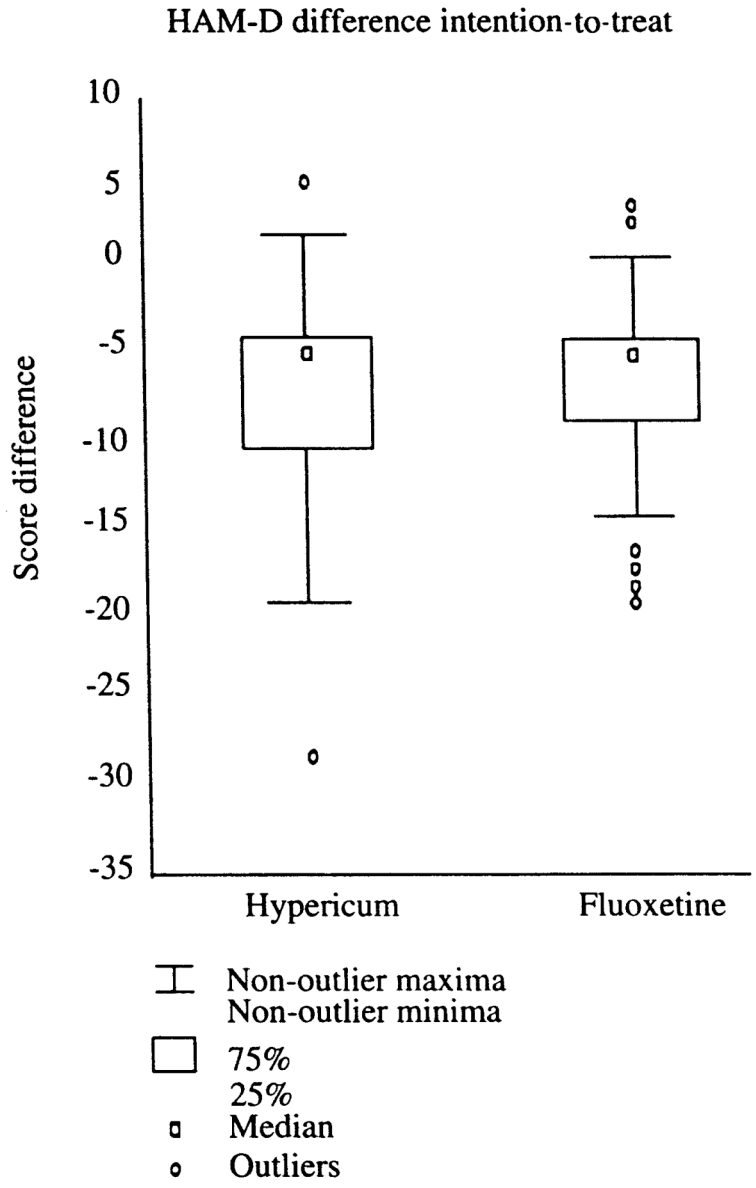
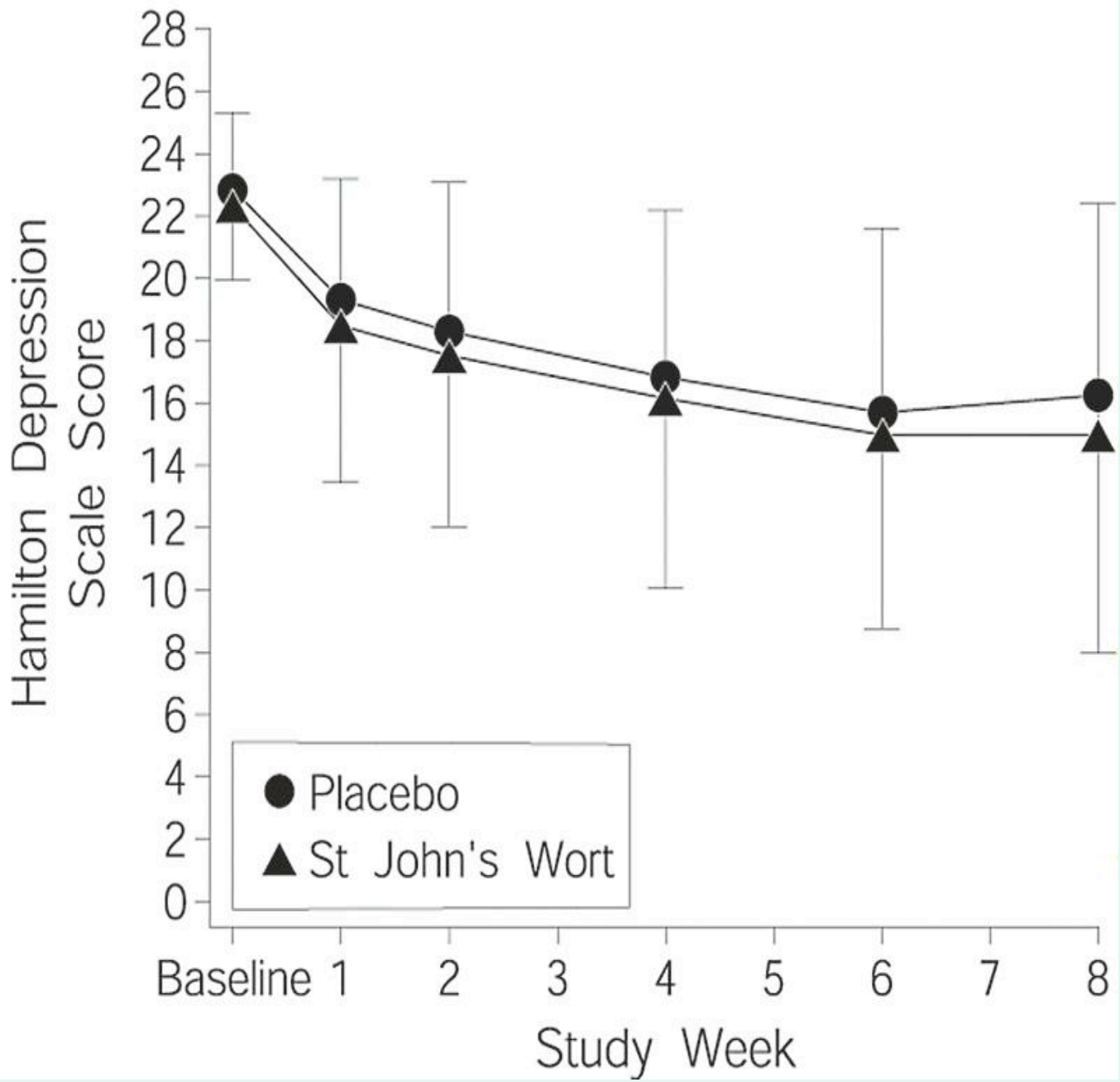


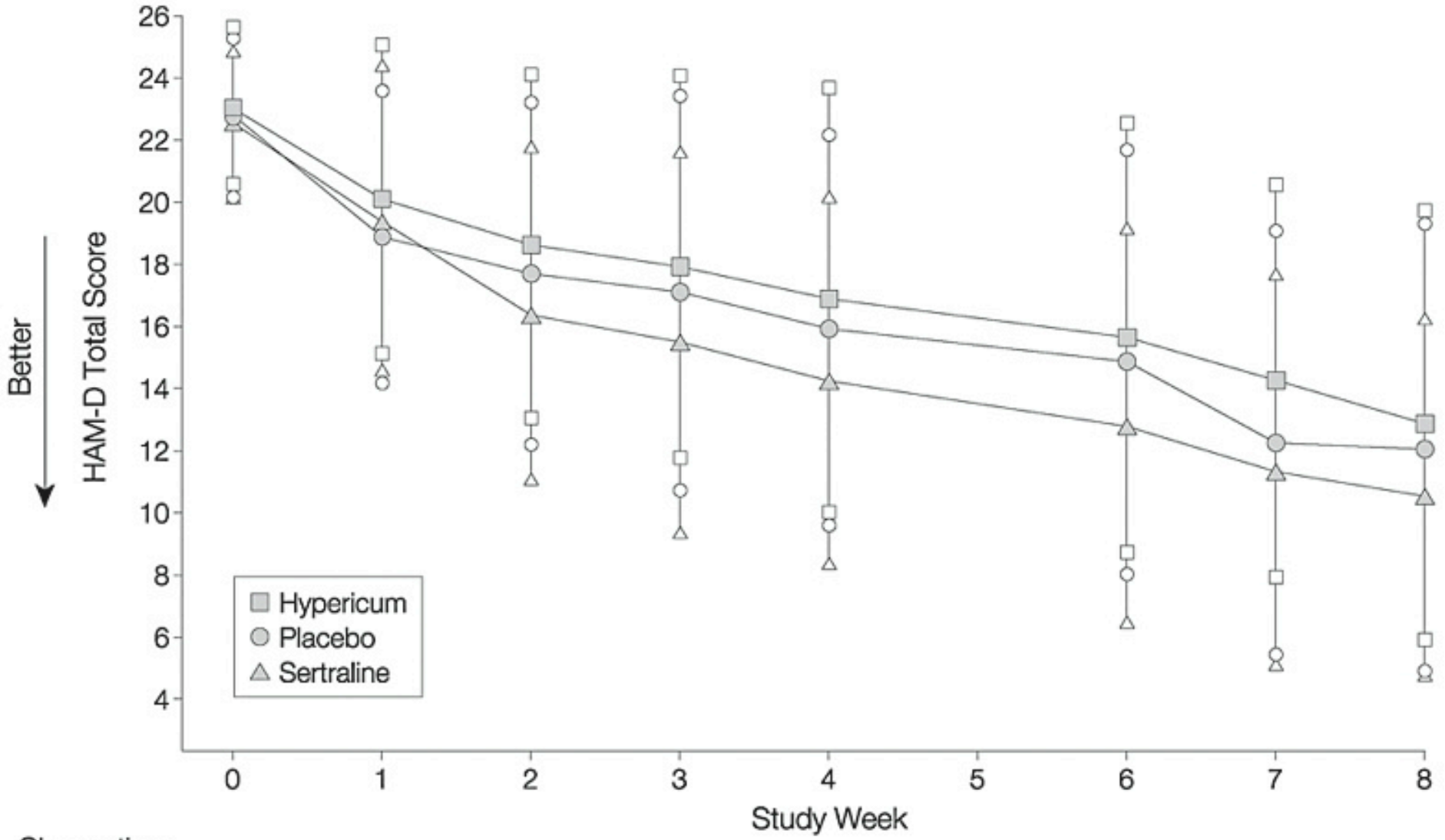
Figure 2. Improvement in HAM-D scores. ITT, intention-to-treat.

Schrader et al., Int J Clin Psychopharmacol 15:61-68,2000



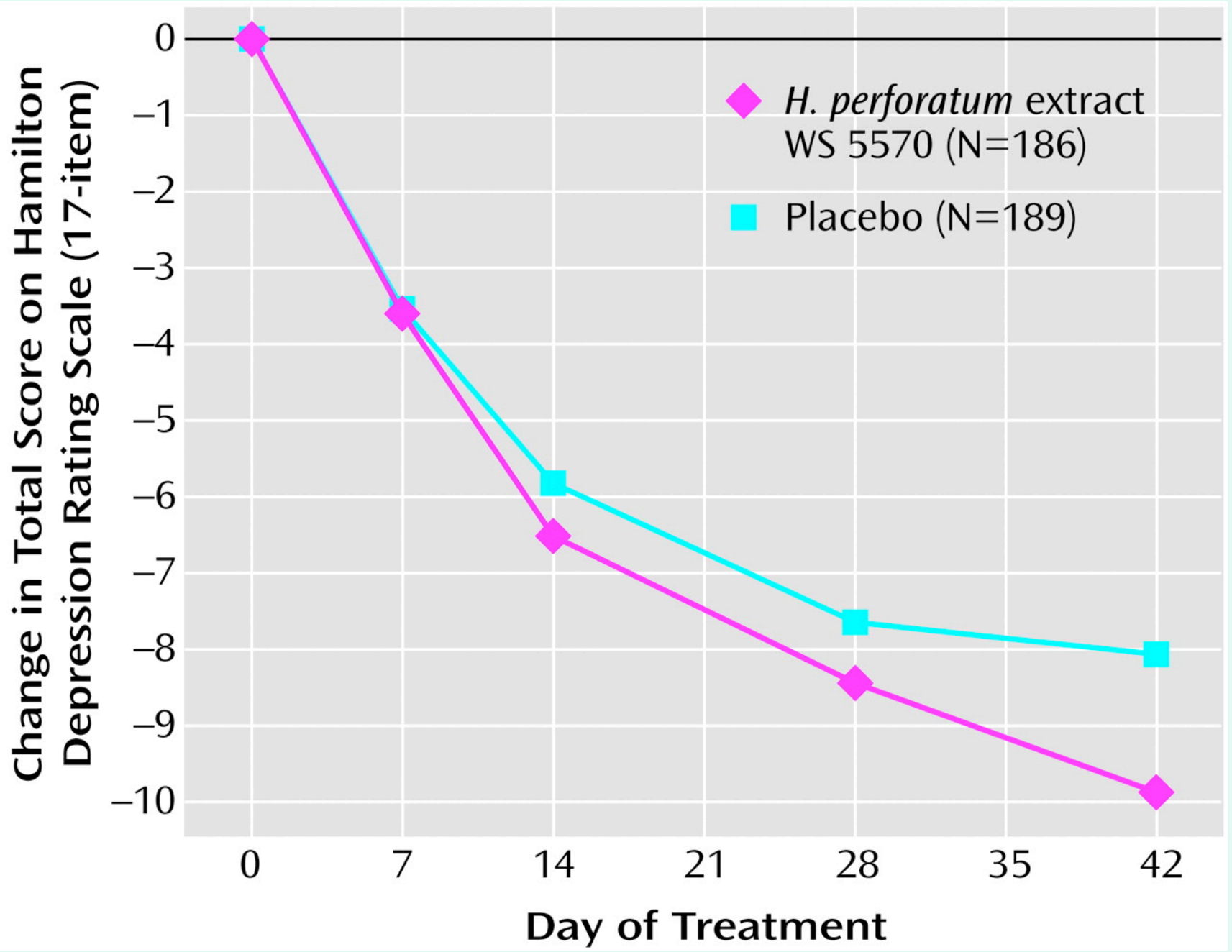
Shelton et al. JAMA 2001, 285:1978-1986

- NIH funded study
  - Duke Univ.
  - N=336 with **major** depression
  - 1/3 SJW 1/3 SSRI 1/3 placebo
  - 3 years



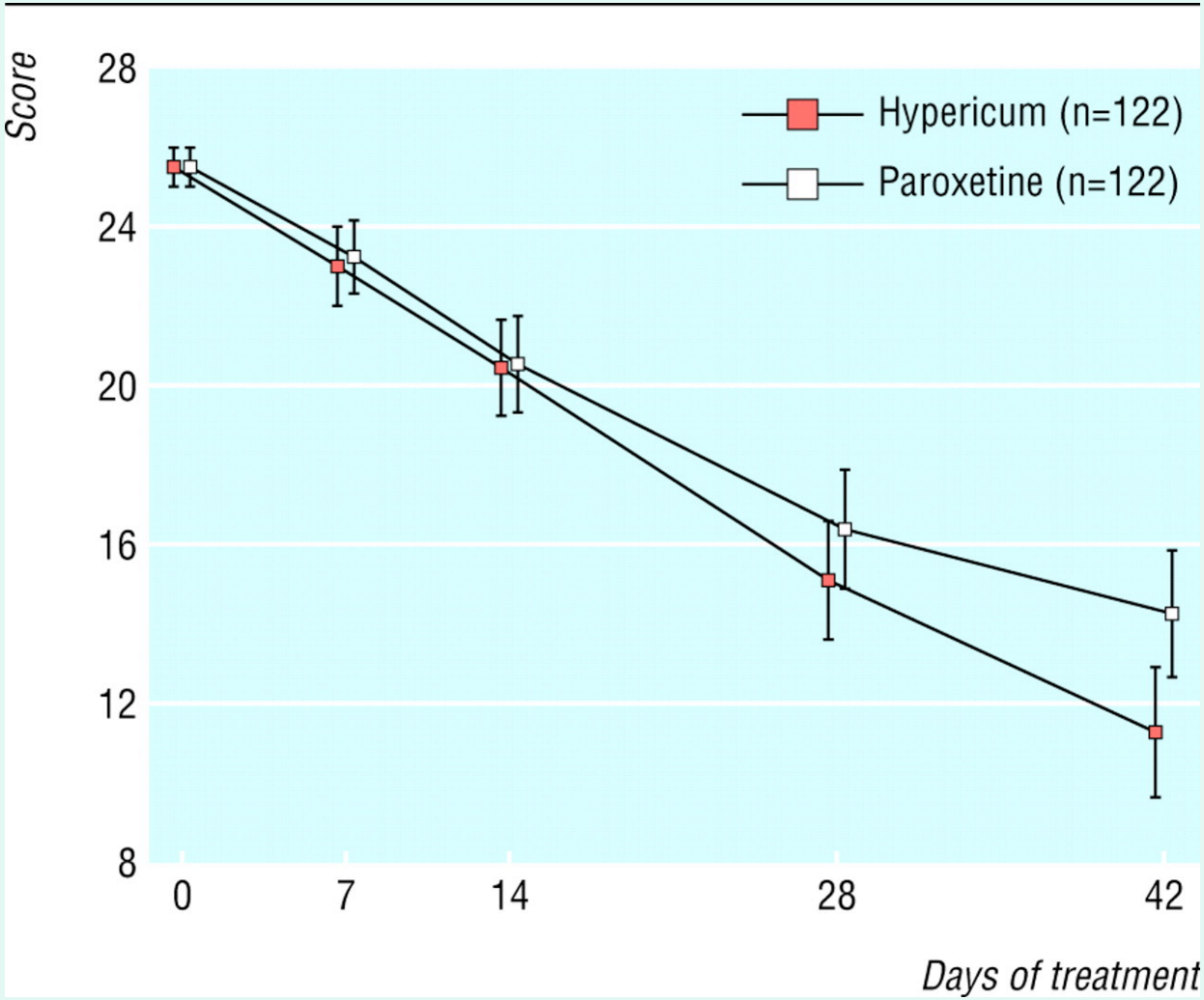
Observations								
Hypericum	113	101	102	100	97	91	82	82
Placebo	116	111	107	94	99	93	84	84
Sertraline	109	99	88	88	87	80	77	77

Davidson et al. JAMA 2002;287:1807-1814



Lecrubier et al. Am J Psychiatry 2002;159:1361 n=375

Fig 2 Total Hamilton depression scores over time (intention to treat analysis, means and 95% confidence intervals)



Szegedi, A et al. BMJ 2005;330:503

Used WS552 containing 5.2% hyperforin

St. John's Wort

- Other Uses: less well documented
  - Seasonal Affective Disorders
    - n=20 SAD patients
    - same decrease in Hamilton depression scale with SJW ± light
  - Hypericin antiviral studies
  - hypericin activity against glioma cells
  - SJW long used to heal wounds
    - plant oil has antimicrobial activity

St. John's Wort

- **adverse**
  - **photosensitivity-animals**
  - **photosensitivity- humans- in high doses is a risk**
    - **1800mg/d + UVA; not at usual doses**
  - **SSRI drugs contraindicated. Additive effects with imipramine**
  - **Open study of 3250, Wolk et al 1994**
    - **0.5% allergic rxns, 0.6% GI, 0.4% fatigue**
  - **SJW is a CYP inducer with herbal/drug interactions documented.**
  - **SJW is a PGP inducer with documented interactions**

St. John's Wort

- **Summary**
  - **Efficacy: good evidence in mild to moderate depression**
  - **Safety: don't combine with other medications unless under close monitoring; possible photosensitivity**
  - **Drug interactions: a problem. Is a P450 inducer and a p-glycoprotein inducer**
  - **Product selection: want standardized extract containing about 0.3% hypericin or 2-3% hyperforin; 300mg TID for treatment; LI160 and WS1172 extracts are the best studied**
  - **Questions remaining include**
    - ***How best to use this herbal given that there are drug interaction problems***

Hypericin and Hyperforin in Eight Brands of St. John's Wort

De Los Reyes and Koda, Am J Health-syst Pharm 59:545-547.2002

Product	hypericin (%)	hyperforin (%)*
Hyperifin	0.29	1.89
PNC	0.12	0.20
Brite-Life	0.22	1.16
ShopKo	0.26	0.05
Shurfine	0.17	0.29
YourLife	0.28	0.19
Nature's Balance	0.03	0.01
Natrol	0.25	0.48

* Usually want 0.3% hypericin and 1-2% hyperforin