A multicentre open clinical trial to assess the tolerability and efficacy of Sage tablets in climacteric women with hot flushes

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Conclusion

A newly developed Sage fresh plant extract in once daily application demonstrated good clinical value in terms of safety, efficacy, and tolerability in the treatment of menopausal hot flushes and climacteric symptoms, validated by statistical analyses and the clinically relevant verdict of patients and physicians who rated efficacy and tolerability good and very good in the majority of cases. The high acceptance perceived is reflecting the demand of this patient group for a herbal alternative that is safe, easy to administer and effective in the treatment of climacteric complaints, hot flushes and excessive sweating in menopause.

Introduction

Sage has been traditionally used as a tonic, against mental and physical exhaustion, hyperhydrosis, and hot flushes in menopause. Whilst most women suffer from menopausal symptoms, mainly hot flushes and insomnia, during the climacteric period , many are reluctant to rely on HRT (1) and inclined to resort to phytotherapeutic treatment options. Based on prior positive response to a sage fresh plant precursor product we developed a holistic thujone-free fresh plant sage extract which we investigated regarding its safety and efficacy in a once daily application of a dosage corresponding to the monographs of ESCOP (2) and commission E (3) in an open clinical trial in menopausal women with hot flushes.

Results

Demographic data

We included 69 women (mean age 56 years) with hot flushes

Efficacy

- Statistically significant decrease of the TSIRHF (total score of the mean number of intensity rated hot flushes)
  - Decrease from 16,9 to 6 intensity rated hot flushes after 8 weeks by 64% to approx. a third.
  - Reduction of number of intensity rated hot flushes by 50% after 4 weeks.
  - Significant decrease ($p < 0.05$) each week compared to previous week (except for weeks 4/5 and 6/7) from week 1 to week 8. With still significant decrease from week 7 to 8, further decreases in longer therapy are likely.

- Statistically significant decrease of the mean total number of hot flushes per day from 9.3 to 3.8 after 8 weeks ($p = 0.0001$). Reduction by 30% already after 2 weeks of therapy ($p = 0.0001$) and by 50% after 4 weeks ($p = 0.0001$). Reduction of:
  - Mild flushes from 3.7±8.4 to 2.0±2.1 ($p>0.05$)
  - Moderate flushes from 3.9±4.6 to 1.5±2.8 ($p = 0.0001$)
  - Severe flushes from 1.4±3.4 to 0.3±0.9 ($p = 0.0001$)
  - Very severe flushes from 0.3±1.2 to 0.0±0.2 ($p>0.05$)

- Statistically significant decrease of the score of the MRS and all subscales:
  - Menopause Rating Scale by about 6.4±0.9 score points from 14.9 to 8.6 ($p < 0.0001$)
  - Somato-vegetative subscale by about 3.3±0.4 score points from 7.6 to 4.3 ($p < 0.0001$)
  - Psychological subscale by about 2.7±0.5 score points from 5.8 to 3.1 ($p < 0.0001$)
  - Urogenital subscale by about 0.3±0.1 score points from 1.5 to 1.2 ($p < 0.01$)

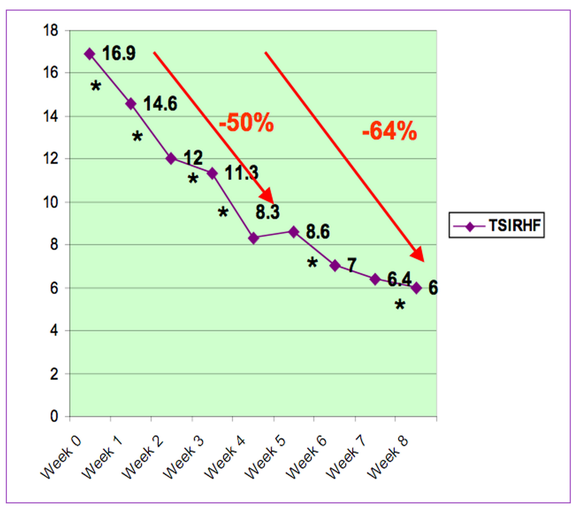

Fig 1 Total score of mean number of intensity rated hot flushes /TSIRHF from week 0 to week 8 (n=69)

The TSIRHF , calculated from the mean number of mild, moderate, severe and very severe hot flushes, is defined by TSIRHF = $\sum$ (mean number of hot flushes of intensity i) * i with i = 1 to 4 (1 = mild, 2 = moderate, 3 = severe and 4 = very severe)

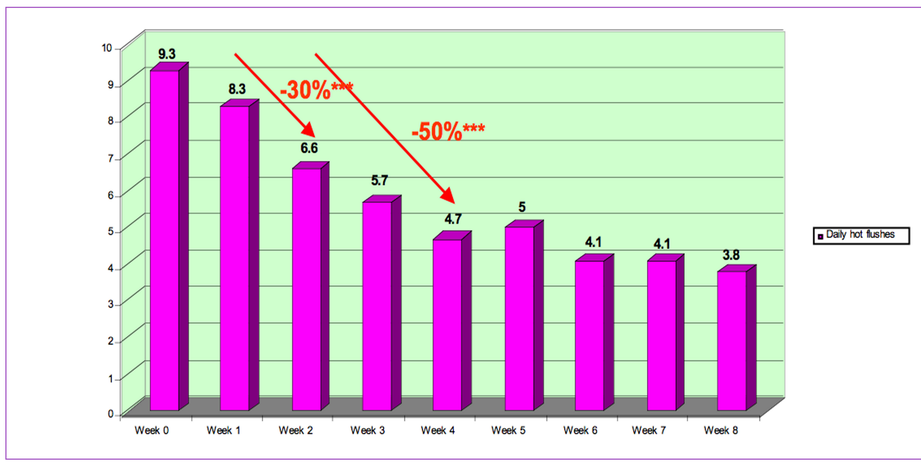

Fig 2 Mean total number of hot flushes per day from week 0 to week 8 (n=69)

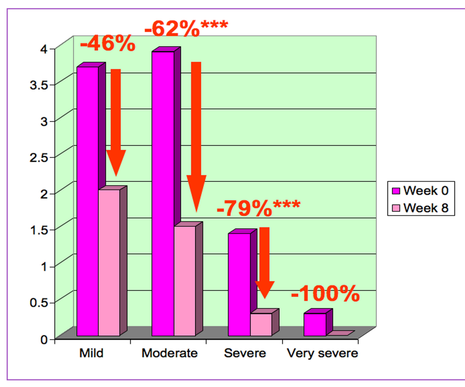

Fig 3 Mean number of total daily hot flushes per intensity group at week 0 and week 8 (n=69)

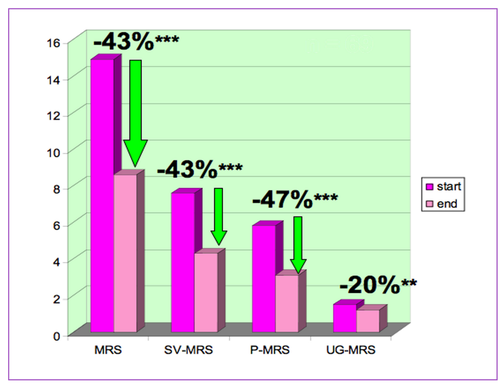

Fig 4 Global MRS score, somato-vegetative (SV-MRS), psychological (P-MRS), and urogenital subscore (G-MRS) before and after treatment (n=69)

Safety

Adverse events

- 10 adverse events occurring in 6 patients were reported, of these only two (abdominal pain and diarrhoea, both of mild intensity) were judged to be related to the study medication.
- Tolerability was rated as very good or good by 90% of physicians and patients.

Laboratory assessments

- The evaluation of the laboratory parameters demonstrated a high degree of safety. No significant change in the mean of leucocyte counts, erythrocyte counts, haemoglobin, hematocrit, MCV, MCH, MCHC, ESR /erythrocyte sedimentations rates, thombocyte counts, ALAT (GPT), AAT (GOT), bilirubin, creatinine , glucose and cholesterol was observed.

Patients and Methods

Multicentric open clinical safety trial

Inclusion criteria

- Women aged 50-65 years
- Menopausal since at least half a year
- With at least 5 hot flushes daily
- No serious illnesses, no other medication, including FS, with an influence on menopausal symptoms within the last month prior to study start

Investigated parameters

Safety (primary objective)

- Safety laboratory parameters at start and end of treatment
- Adverse events during treatment period
- Tolerability assessment by physician and patient at the end of treatment

Efficacy (secondary objective)

- Number and intensity * of hot flushes per day from week 0 (without medication) to week 8 (patient diary) * according to Sloan J (4)
- TSIRHF
- Global Score, and somato-vegetative, psychological and urogenital Subscores of Menopause Rating Scale at begin and end of treatment
- Global assessment of efficacy by physician and patient

Treatment regimen

1 x 1 tablet with 280 mg spissum extract, corresponding to 3400 mg Sage fresh plant tincture (DER 1:17) daily for 8 weeks. The holistic sage extract is thujone free (α thujone < 1 ppm).

MRS Subscales		Symptom	Score	none 0	mild 1	moderate 2	severe 3	very severe 4
Somato-vegetative SV-MRS	1	Hot flushes, sweating (episodes of sweating)						
	2	Heart discomfort (unusual awareness of heart beat, heart skipping, heart racing, tightness)						
	3	Sleep problems (difficulty in falling asleep, difficulty in sleeping through, waking up early)						
Psychological P-MRS	4	Depressive mood (feeling down, sad, on the verge of tears, lack of drive, mood swings)						
	5	Irritability (feeling nervous, inner tension, feeling aggressive)						
	6	Anxiety (inner restlessness, feeling panicky)						
	7	Physical and mental exhaustion (general decrease in performance, impaired memory, decrease in concentration, forgetfulness)						
Urogenital UG-MRS	8	Sexual problems (change in sexual desire, in sexual activity and satisfaction)						
	9	Bladder problems (difficulty in urinating, increased need to urinate, bladder incontinence)						
	10	Dryness of vagina (sensation of dryness or burning in the vagina, difficulty with sexual intercourse)						
Somato-vegetative SV-MRS	11	Joint and muscular discomfort (pain in the joints, rheumatoid complaints)						

Table 1 MRS - the Menopause Rating Scale
(Berlin Center for Epidemiology and Health research)

Literature

1) Genazzani A, Schneider H, Panay N, Nijland E. The European Menopause Survey 2005: Women's perceptions on the menopause and postmenopausal hormone therapy. Gynecological Endocrinology, Volume 22, Number 7, July 2006 , pp. 369-375

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