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Is Extract ERr731 from the Rheum Rhaponticum Effective in Relieving Menopausal Symptoms in Women Aged 45 to 55 Years of Age?

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Is extract ERr731 from the *Rheum rhaponticum* effective in relieving menopausal symptoms in women aged 45 to 55 years of age?

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ABSTRACT

OBJECTIVE: To determine whether ERr 731 extract from the *Rheum rhaponticum* plant is effective in relieving symptoms of menopausal symptoms in women aged 45 to 55 years of age

STUDY DESIGN: Review of all English language double blind randomized controlled trial studies from 2006 to 2009.

DATA SOURCES: Randomized, controlled, double-blind, placebo controlled clinical trials comparing extract ERr731 to placebo were found in MEDLINE, OVID, and COCHRANE databases.

OUTCOMES MEASURED: All three trials measured Menopause Rating Scale II. Also determined in the review is the severity and number of hot flushes, and also a change in the quality of life. Results for anxiety used the HAMA scale and results for changes in quality of life and well being were assessed on the Menopause specific Quality Of Life, Women's Health Questionnaire, diary reports and the psychological general well being index.

RESULTS: All three trials showed results demonstrating significant results using extract ERr731 to decrease severity and number of hot flashes, increase the quality of life and also decrease overall menopause symptoms in women aged 45 to 55 years old. Participants in Heger et al reported adverse events but no serious adverse events.

CONCLUSIONS: The results of the three trials show that extract ERr 731 is effective in reducing symptoms and severity of symptoms in menopause compared to placebo. The extract however, has not been evaluated by many other studies or the FDA therefore true side effects and risks are not determined.

KEY WORDS: Menopause, climacteric, hot flushes.

INTRODUCTION

Menopause is the transition period that occurs in all women usually between the ages of 45 and 55 when menstruation eventually stops. It is a natural biological termination of the ability to reproduce in the female population where eggs are no longer released from the ovaries. Some of the most common symptoms resulting include hot flushes and mood swings which women search for treatments to find relief. Current treatments are available but aren't always effective or they have significant side effects. This paper evaluated randomized controlled double blind clinical trials comparing ERr731 extract to placebo in alleviating symptoms of menopause.

Relieving menopausal symptoms is common to encounter in all fields of PA practice. The majority of women experience some symptoms within their lifetime at an average age onset at 51. About 85% of women have symptoms for 1 year, 25% for 5 years and about 15% of women have symptoms for 15 years or more (Manson , 2010). In the transition from perimenopause to menopause, symptoms can disrupt the quality of life. About one-third of women will consult a doctor annually because of menopausal symptoms but definite cost is unknown (Gunthrie 2003). After the age of 35, ovarian mass and fertility decline. The process of depletion of primary follicles begins before birth and continues steadily until menopause. In perimenopause, intervals between menstrual cycles shorten by about 3 days due to an accelerated follicular phase. Follicle-stimulating hormone (FSH) levels rise, from altered folliculogenesis and reduced inhibin secretion. The consistently high FSH and low estradiol levels cause irregular hormone levels. During the transition into menopause, estradiol levels fall and estrone levels are preserved. FSH levels increase more than luteinizing hormone (LH) levels, due to the loss of inhibin, and estrogen feedback. The change in hormones and age give rise to vasomotor symptoms (hot

flushes), menstrual cycle alterations, vaginal dryness and atrophy, sleep disturbances, mood changes, skin hair and nail changes, and osteoporosis.

Treatments for menopause symptoms include hormone replacement therapy. The replacement of hormones can involve estrogen only, progestin only or a combination of both. There are oral combinations including Prempro and Premphase, patch combinations including Estraderm, Climara Pro or Combipatch. Other forms of hormone replacement include vaginal suppositories, which are estrogen hormone only, including Estrace and Premarin. Other alternate treatments include Selective Serotonin Reuptake Inhibitors (SSRI), soy, Black Cohosh, St. John's Wart, 1200mg Calcium per day, and 400-800mg Vitamin D per day.

The method of treatment being proposed is that hormone replacement therapy is effective but has adverse side effects making them unsuitable for many patients. Some of the side effects include an increased risk of blood clot formation, cancer (especially breast cancer), cerebrovascular accidents and heart disease. The alternative treatments are not as affective and also cause adverse reactions and drug interactions including headache, dizziness, nausea, sedation, constipation, allergic reactions and drug interactions. One of the major side effects is the interaction of St. John's Wort and the possible adverse reaction with inducing metabolism of P450 drugs. However, the extract ERr731 from the *Rheum rhaponticum* may provide satisfactory reduction in symptoms without any serious adverse effects.

OBJECTIVE

The objective of this systematic review is to determine whether or not "Is extract ERr731 from the *Rheum rhaponticum* effective in relieving menopausal symptoms in women aged 45 to 55 years of age?" Although previous studies have shown some efficacy in hormone replacement

therapy and other alternative treatments, extract ERr731 from the *Rheum rhaponticum* plant has not previously been tested and thus efficacy of this extract is unknown.

METHODS

Each of the three studies selected for this review meet the following criteria: The population included females aged 45-55 with climacteric complaints and a Menopause Rating Scale II score of $\geq$ 18 who have an irregular menstrual cycle lasting for the past 12 months and/or their last menstruation was at least 3 months ago but no longer than 12 months ago. Exclusion criteria includes women who have regular menstrual cycles 3 months prior, PAP smear of class III/IV endometrial hyperplasia, concomitant medication that might impair the trial results, abnormal endometrium and breast, presence of concomitant disease, alcohol, smoking, caffeine, and a body mass index less than 18 kg/m^2 or greater than 30 kg/m^2. The intervention used in the studies was 4mg tablets of ERr731 extract from the *Rheum rhaponticum* plant in tablet form. The treatment groups were compared to control groups given a visually matched placebo. The main outcomes which were measured in a prospective, randomized, double-blind placebo controlled clinical study were anxiety, quality of life and hot flushes. All English written articles were searched using key words like menopause, climacteric, and hot flushes on OVID, Medline and Cochrane databases. Each article was selected based on patient oriented evidence that matters (POEMS) and also were published in peer-reviewed journals between 1996 and the present. Table 1 includes the demographics of the 3 clinical trials which met the previously listed inclusion criteria. Statistics reported include p values < 0.05 indicating clinical significance.

A.) Table 1 - Demographics & Characteristics of included studies

Characteristics of studies included in systematic review of the effectiveness of ERr731 extract from the root of *Rheum rhaponticum* in the treatment of menopausal symptoms.							
Study	Type	#	Age yrs	Inclusion Criteria	Exclusion Criteria	W/D	Interventions
Heger et al.	Multicenter prospective double-blind, placebo controlled, RCT	110	45-55	Women with climacteric complains Menopause Rating Scale II (MRS II) of more than 22 points 45 to 55 years old who have an irregular menstrual cycle lasting for the past 12 months and/or their last menstruation was at least 3 but no longer than 12 months ago.	Regular menstrual cycles 3 months prior. PAP smear of class III/IV, endometrial hyperplasia, concomitant medications that might impair the trial results.	64	1 enteric coated tablet of ERr731 extract daily for 12 weeks
Kaszkin - Bettag 2007	Multicenter prospective double-blind, placebo controlled, RCT	109	45-55			64	Enteric coated tablets of 250 mg of ERr731
Kaszkin - Bettag 2009	Multicenter, prospective, double-blind, placebo controlled, RCT	112	45-55	Women aged 45 to 55 years old with irregular menstruation cycles during the past 12 months or last menstrual period $\geq$ 3 but $\leq$ 12 months ago. Menopausal Rating Scale total score $\geq$ 18 points indicating moderate to severe menstrual symptoms.	Abnormal endometrium and breast, presence of concomitant diseases, use of predefined medications, pretreatment of menopausal symptoms alcohol, smoking and caffeine, and a body mass index less than 18 kg/m^2 or over than 30 kg/m^2	19	Enteric coated tablets containing 4 mg of *Rheum rhaponticum* dry extract

[*Ref = Reference number. See reference page for list of papers cited]

OUTCOMES MEASURED

Outcomes were measured using patient completed severity score surveys or questionnaires on anxiety, quality of life, or hot flushes. In the article by Heger, et al. the outcomes were measured using a diary, MRSII, and the menopause specific quality of life (MENQOL) score completed by the participants. Kaszkin-Bettag et. al (2007) use the Hamilton Anxiety Scale (HAMA), Menopause Rating Scale II (MRSII), the psychological general well being index, and Women's Health Questionaire (WHQ) all completed by the participants to measure their outcomes. In the article by Kaszkin-Bettag et al. (2009) the outcomes were measured using the MRS II and a diary completed by the participants also.

RESULTS

The randomized controlled trials selected are double blind, prospective clinical trials analyzed with intention to treat and all participants in the trials who meet inclusion criteria received the same ERr731 treatment or placebo, see table 1 for details. Some data from each study is reported in dichotomus data yet other important data was unable to be converted into dichotomous.

In Heger Et al, a total of 55 participated for the placebo group and 54 participants were involved in the ERr731 treatment group. Only7 participants from the control trial and 39 participants from the ERr731 treatment group finished the experiment. Discontinuation in the treatment group totaled 16. One for lack of efficacy, 3 for violation of the smoking ban, 3 for adverse events, 2 for organizational reasons and 7 for other reasons not listed. In the placebo group, a total of 48 discontinued the study. Thirty-one discontinued for lack of efficacy, 1 for violation of the smoking ban, 1 for adverse events, and 16 for other reasons. The Heger et al study measured menopausal symptoms throughout the studying using the Menopausal Rating

Scale II, which includes 11 symptoms assessed on a 6-point rating scale from 0=not present to 5 being most severe and a maximum score of 55 {17 Heger,M. 2006;}. Table 2A shows results from the MRSII scores. On day 0 the treatment and placebo group had similar scores on the MRSII, 34.0± 5.6 and 27.9± 8.7 respectively. By the end of the study, there were only 46 participants in the ERr731 group but a significant decrease in the average MRSII score to 13.5 ± 6.3 showing a reduction in about 20 points. The placebo group only had 12 participants who completed the study who reported an average MRSII score of 27.9 ± 8.7 {17 Heger,M. 2006;}. Table 2B shows results from the MENQOL, the Menopause-specific quality of life. From the participants' diaries the MENQOL score was calculated on 4 domains: vasomotor, psychological, physical and sexual. The total score in each domain ranges from 1 to 8 and a lower score indicates a better quality of life. In table 2B, the average MENQOL score for each group is listed on day 0 and day 84. Both groups had similar scores when beginning the assessment, however, by day 84 the ERr731 score decreased more than the placebo group. Seventeen adverse events occurred in 16 women during the study; events included back pain, intercostals neuralgia, dizziness, viral infection of the upper respiratory tract, duodenal ulcer, cardiomyopathy, dysuria, weight gain, endometrium dysplasia and uterofibroma {17 Heger,M. 2006;}. Table 2D shows results for the adverse events and no events were considered to be related to the investigation medication {17 Heger,M. 2006;}.

Table 2 A. Heger et al.: Severity scores on the MRSII

Time	Group	#	MRS II	95% CI	SS
Day 0	ERr731	54	34.0 ± 5.6	32.516-35.558	P < 0.001
	Placebo	55	32.6 ± 4.8	31.329-33.944	
Day 84	ERr731	46	13.5 ± 6.3	11.621-15.379	P < 0.0001
	Placebo	12	27.9 ± 8.7	22.381-33.452	

Table 2 B. Heger et al. reference #1: Reduction in severity scores on the Menopause-specific Quality of Life Questionaire (MENQOL)

Time	Group	Total	SS
Day 0	ERr731	4.72	P < 0.05
	Placebo	4.46	
Day 84	ERr731	2.69	P < 0.05
	Placebo	3.36	

Table 2 C. Heger et al. reference #1: Reduction in the number and severity of hot flushes during the past 24 hours recorded in participant diaries. (p<0.0001).				
Time	Group	Total hot flushes /day	Severity	Number of specific hot flushes
Baseline Day 0	ERr731 n=44	16.2 ± 7.7	Slight	7.6 ± 2.5
			Moderate	5.5 ± 3.6
			Severe	3.1 ± 4.7
	Placebo n=46	14.8 ± 6.9	Slight	7.4 ± 4.3
			Moderate	4.6 ± 3.2
			Severe	3.1 ± 6.9
Decrease in number on Day 28	ERr731 n=43	-5.5 ± 4.4	Slight	-0.2 ± 2.8
			Moderate	-2.8 ± 3.1
			Severe	-2.6 ± 4.6
	Placebo n=42	0.0 ± 3.2	Slight	-0.6 ± 2.8
			Moderate	0.2 ± 2.5
			Severe	0.3 ± 3.0

Table 2D. Heger et al. total adverse events.					
Group	Participants with adverse events	RR	RRI	ARI	NNH
ERr731	8/54= 0.1481 = 14.81%	1.02 = 102%	0.0186 = 1.86%	0.0027 = 0.27%	370.3 = 370
Placebo	8/55 = 0.1454 = 14.54%				

In Kaszkin-Bettag et al, 2007, the study focused on decreasing anxiety and the well being of women after the 84 day trial of ERr731 extract compared to the placebo. The Hamilton Anxiety Scale was used to determine a baseline and change in anxiety symptoms. The rating scale determines the severity of anxiety symptoms consisting of 14 items like muscle aches and pains, depressed mood, fears, insomnia, and tension. Each of the categories are rated on a 0 (not present) to 5 (severe) {16 Kaszkin-Bettag,M. 2007;}. At baseline, day 0, the total HAMA score was similar between both placebo and treatment group. The ERr731 groups' score was 27.5 ± 6.8 and the baseline score for the placebo group was 25.1 ± 6.0. On day 84, the group treated with ERr731 had an average score of 9.4 ± 4.2. The placebo group's HAMA average total at the end of the trial decreased to 21.6 ± 8.6. (See table 3a) {16 Kaszkin-Bettag,M. 2007;}. Another measurement to determine the success of ERr731 was the Psychological General Well-Being Index. It is a self-administered quality of life assessment. Table 3C shows the results and

changes in the index reported by participants. As referenced in the table, Day 0 scores were "low spirits mostly" or "I have been up and down in spirits a lot". On day 84, 59.3% of participants reported being in good spirits mostly from the ERr731 treatment group compared to 7.3% of the placebo group {16 Kaszkin-Bettag,M. 2007;}. Kaszkin-Bettag et all 2006 also used the MRSII to measure the changes in anxiety in particular for the study. Table 3D represents differences in slight and severe anxiety at baseline and at the end of the trial. The percent of severe anxiety in both treatment and placebo groups was more significant in number. The participants that experienced severe anxiety was 48.1% in the treatment group and 45.5% in the placebo group. At the end of the study, the percent of women with severe anxiety in the treatment group was 1.9%, and in the placebo group it was 32.7% {16 Kaszkin-Bettag,M.2007;}.

Table 3A. Kaszkin-Bettag et al. 2007. Changes in the HAMA total score in women from the ERr731 and placebo groups. (P<0.0001)

Time	Group	#	HAMA total score
Day 0	ERr731	54	27.5 ± 6.8
	Placebo	55	25.1 ± 6.0
Day 84	ERr731	46	9.4 ± 4.2
	Placebo	12	21.6 ± 8.6

Table 3B. Kaszkin-Bettag et al. 2007. Women's Health Questionnaire (WHQ) result.

Time	Group	WHQ score
Day 0	ERr731	83.5± 10.0
	Placebo	85.5 ± 7.7
Day 84	ERr731	105.9 ± 16.6
	Placebo	77.0 ± 25.5

Table 3C. Kaszkin-Bettag et al 2007. Psychological General Well-Being Index results.

Time	Group	Participants	Result	RR	RBI	ABI	NNT
Day 0	ERr731	21/54 (38.9%)	"Low spirits mostly"	1.78	0.784 = 78.4%	0.171 = 17.1%	5.85 = 6
	Placebo	12/55 (21.8%)					
	ERr731	31/54 (57.4%)	" I have been up and down in spirits a lot"	0.790	-0.267 = -26.7%	-0.153 = -15.3%	-6.54 = -7
	Placebo	40/55 (72.7%)					
Day 84	ERr731	32/54 (59.3%)	"In good spirits mostly"	8.12	7.12 = 712%	0.52= 52%	1.92 = 2
	Placebo	4/55 (7.3%)					

Kaszkin-Bettag et al. 2009 measured a change in overall menopausal symptom change through the MRS scale and also looked at number of hot flushes women experienced in a 24-hour time span. Table 4A shows the change in MRS score from day 0 to 84 in the ERr731

(decreased by 14.6 on the MRS scale) and also demonstrated the change in number of hot flushes women experienced per day {14 Kaszkin-Bettag,M. 2009;}.

Table 3D Kaszkin-Bettag et al 2007 . Anxiety symptoms of the menopause rating scale II.

Time	Group	Severity	#	%	RR	RBI	ABI	NNT
Day 0	ERr731	Slight	3/54	5.6	7.727	6.745	0.371	2.695
	Placebo	Slight	3/55	5.5				
	ERr731	Severe	26/54	48.1	1.057	0.057	0.026	38.46
	Placebo	Severe	25/55	45.5				
Day 84	ERr731	Slight	12/54	22.2	1.11	0.11	0.022	45.45
	Placebo	Slight	11/55	20.0				
	ERr731	Severe	1/54	1.9	0.058	-0.942	-0.308	3.25
	Placebo	Severe	18/55	32.7				

Table 4A shows the change in MRS score from day 0 to 84 in the ERr731 (decreased by 14.6 $\pm$ 5.1) and the placebo group (decreased by (2.9 $\pm$ 4.3). Table 4B, displays the decrease in average number of hot flashes experienced by women throughout the intervention {14 Kaszkin-Bettag,M. 2009;}. Table 4C gives the evidence that a clinician needs to treat 28 women in order to harm one more in the treatment group.

Table 4A Kaszkin-Bettag. Et al. 2009. MRS total score changes from base line to day 84.

Time	Group	MRS total score
Day 0	ERr731	27.0 $\pm$ 4.7
	Placebo	27.0 $\pm$ 5.3
Decrease in total score on Day 84	ERr731	-14.6 $\pm$ 5.1
	Placebo	-2.9 $\pm$ 4.3

Table 4B. Kaszkin-Bettag et al. 2009. Number of hot flashes reported in diaries by participants.

Time	Group	Number of hot flushes
Day 0	ERr731	11.4 $\pm$ 5.8
	Placebo	12.1 $\pm$ 6.0
Day 84	ERr731	2.8 $\pm$ 2.8
	Placebo	11.4 $\pm$ 6.8

Table 4C. Adverse event reports.

Group	Number of patients with AEs	RRI	ARI	NNH
ERr 731	5/56 = 0.0892 = 8.92%	0.664 = 66.4%	0.0356 = 3.56%	28.0
Placebo	3/56 = 0.0536 – 5.36%			

DISCUSSION

The randomized controlled trials in this review of extract ERr 731 in the treatment of menopausal symptoms showed that the medication can safely treat the symptoms and improve

quality of life. The reduction of menopausal symptoms, especially anxiety and hot flushes, and an increase in quality of life was consistently demonstrated within all 3 clinical trials. Since there is numerous data collected, a reference for the abbreviation meanings is helpful to obtain more information from the charts. Risk ratio (RR) is the ratio of the probability of developing an outcome in a specified time among those who received the treatment compared with the probability of developing the outcome among those who didn't receive the treatment. Relative risk increase (RRI) and absolute risk increase (ARI) are used to determine the increase risk of a bad thing happening. Alternatively, relative benefit increase (RBI) and absolute benefit increase (ABI) determine the probability of a good thing happening. Finally, the number needed to harm (NNH) or number needed to treat determines how many people need to be treated in order to have 1 increase in a bad event or 1 increase in a good event respectively. Heger et al. and Kaszkin-Bettag 2009 reported adverse events. The calculations determined from Table 2D demonstrate that for every 370 women who had the experimental treatment, there was 1 more incidence of adverse reaction in the group that had a placebo, even though the adverse events were not necessarily related to the treatment {17 Heger,M. 2006;}. . In Kaszkin-Bettag et al 2006, showed similar results for successful treatment. In reference to table 3c the number needed to treat decreased from 6 to 2 by the end of the trial. Therefore, a clinician would need to treat only 2 mothers to relieve menopausal symptoms, therefore increasing the quality of life. The most impressive result from table 3D shows changes in anxiety, specifically by the end of the trial, a clinician would need to treat 3.25 women in order to have one more decrease in severe anxiety compared to baseline where 38.46 women needed treatment before there was one reduction in severe anxiety. Even though the extract seems effective, it had not been evaluated by the food and drug administration, it is only available online through one distributer. The

limitations in the clinical trials include the discontinuation in treatment within both groups in all three studies. In Heger et al, and Kaszkin-Bettag et all 2006, 39 women in the treatment group and only 7 women in the control group completed the study. However, all participants, 54 from treatment and 55 from control group were followed up in a 48 observational study. In Kaszkin-Bettag et all 2009, 47 women in the treatment group and 46 women in the control group completed the study as planned. With the participants who were lost, all were entered into a 52 week observational study for follow up.

CONCLUSION

The studies reviewed demonstrate that extract ERr 731 is effective in reducing menopausal symptoms and increasing the quality of life for women suffering from symptoms. However, there are not many trials with varying amounts of extract. In all 3 clinical trials reviewed, 4mg tablets were used. Future studies should focus varying treatment dosages and treatment start time to determine if symptoms could be prevented or present with minimal severity. Table 1 shows the inclusion and exclusion criteria which is significant and challenging for an entire population to follow. Future studies should have trials on women who do smoke, drink, have dysplasia and other exclusion criteria that were listed to make sure that more women could take the treatment and be successful rather than a small subset of women. Finally, the studies reviewed for this paper were all completed in Germany, for completeness, a study should be conducted in the United States to determine if the extract could reduce physical and mental parameters of menopausal symptoms within a different culture.

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