Toward Therapeutics for Symptom Clusters during the Menopausal Transition and Early Postmenopause: A Systematic Review

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Background

- Most women experience multiple co-occurring symptoms (clusters) during the menopausal transition and early postmenopause
- Clinical trial reports of hot flash therapies often omit co-occurring symptoms as outcomes
- Systematic reviews of therapeutics for symptoms have focused almost exclusively on a single symptom: hot flashes
- Although most investigators have focused systematic reviews on hormonal therapy, an increasing number are studying non-hormonal therapies

Purpose

Systematically review clinical trials of

Traditional East Asian Medicine,

Herbal therapies,

Soy and isoflavone preparations, and

Mind-body therapies for managing symptom clusters during the menopausal transition and early postmenopause

Methods

- No published reviews of multiple co-occuring symptoms in the menopause literature
- Experienced research librarian searched for randomized controlled trials reported in English between 2004 and 2012
  - PubMED/Medline,
  - CINAHL Plus,
  - PsycInfo,
  - Cochrane Database of Systematic Reviews, Cochrane Central Register of Controlled Trials,
  - Web of Science,
  - EMBASE, AMED, and
  - Alt-Health Watch

Abstracts: Inclusion Criteria

- non-pharmacologic therapy tested
- control or comparison group used
- randomization to study group
- hot flashes as an outcome measure
- full length English publications available for review
- Identified 151 abstracts for which full text publications were reviewed

Full Text Review: Inclusion Criteria

- at least one non-pharmacologic treatment group
- self reported hot flashes as outcome plus 1 other symptom of interest as outcome
- no current breast cancer or no current breast cancer treatment
- no current SERM treatment
- sample age 40 or older and/or irregular cycles or PM regardless of age

Search Results

- 1193 abstracts identified
- 58 reports of trials examining effectiveness of therapies on hot flashes and at least one additional symptom of interest were identified
- 11 trials of Traditional East Asian Medicine (13 reports)
- 17 trials of herbal therapies (17 reports)
- 17 trials of soy-isoflavones (n reports)
- 8 trials of mind-body therapies (10 reports)

Results: TEAM/TCM

- 13 reports of controlled clinical trials of TCM therapies
  - 8 Acupuncture,
  - 4 Chinese Herbal Medicine (CHM),
  - 1 Moxibustion (“Moxa”)

Results: TEAM/TCM

- Of 8 acupuncture trials, 5 reports indicated improved hot flashes, 1 of hot flashes, sleep, and pain, and 1 of hot flashes and mood symptoms
- Use of sham acupuncture produced significant treatment effects
- Of 4 CHM trials, 2 reports indicated improved hot flashes: Zhi Bai di huang improved hot flashes and mood symptoms and Kun Bao Wan improved hot flashes, sleep, mood, and pain symptoms
- Moxibustion trial indicated improved hot flashes, mood, and pain symptoms

Results: Herbal Therapies

- 17 studies of herbal therapies
  - 7 black cohosh
  - 2 black cohosh mixed with other herbs
  - 8 other herbals (Pueraria mirifica, Rheum rhaponticum, herbal medicine, French maritime pine bark, Diascorea alata, and femal)





Results: Herbal Therapies

- Of 7 trials of black cohosh, 2 reports indicated relief of hot flashes, but only one relieved hot flashes, sleep and mood symptoms
- Of 2 black cohosh and herbal mixtures trials, black cohosh and St. John's wart relieved hot flashes and mood symptoms and black cohosh and female Phyto complex relieved hot flashes and sleep symptoms
- Of 8 other herbal preparations studied, 5 indicated relief of hot flashes
- These trials indicated Rheum rhaponticum (2 trials) relieved hot flashes, sleep, mood, and pain symptoms; French maritime pine bark relieved hot flashes, sleep, mood, pain, and cognitive symptoms

Results: Soy/Isoflavones

17 Soy, Isoflavone, & Amino Acid RCTs

5 Soy protein

7 Isoflavone

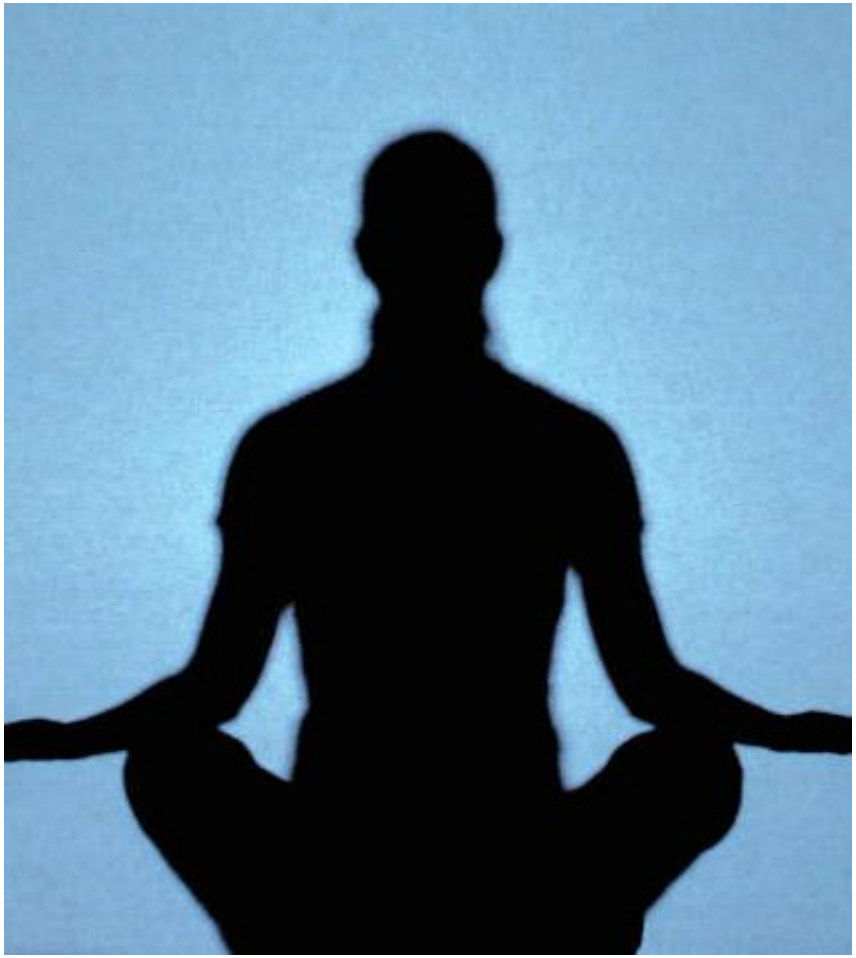
2 Amino Acid

3 Mixtures

Results: Soy and Isoflavones

- Of 5 soy trials, 2 reports indicated improved hot flashes and one improved hot flashes and mood symptoms
- Of 7 isoflavone trials, 5 indicated improved hot flashes, and one improved hot flashes, sleep, cognitive symptoms, mood and pain (red clover)
- Of other Isoflavone trials, 2 reports of improved sleep, 2 of improved mood, and 2 of improved pain
- 2 amino acids tested did not relieve hot flashes

Results: Mind-body therapies



- 9 reports of 8 trials of mind-body therapies
  - 6 Physical activity/exercise
  - 2 relaxation therapies
  - 2 yoga (included as a comparison group in a walking study)

Results: Mind-Body Therapies

- Of 6 physical activity trials, only 1 indicated improved hot flashes; 1 improved mood and 1 improved pain symptoms
- Of 2 relaxation therapy trials, neither indicated improved hot flashes, but mindfulness-based stress response training improved sleep and mood symptoms
- 1 trial of Yoga indicated significantly improved hot flashes and cognitive symptoms (more than exercise)

Challenges in Studying Symptom Clusters as Outcomes in Clinical Trials

- Most investigators did not include symptom clusters in the frameworks for their studies
- Most did not include measures that were homogeneous scales for symptom groups of interest (e.g. mood, pain, sleep)
- Most did not report individual symptom outcomes allowing clear identification of effects
- Most studies included fewer than 100 participants

Conclusions and Recommendations

- Investigators should be encouraged to report treatment effects in ways that allow clinicians to consider symptom clusters when prescribing therapies
- Clinicians need to consider a matrix of symptoms as a basis for prescribing therapy

Potential Benefit: Symptom Cluster Management Matrix to Guide Selection of Therapies (for illustrative purposes only)

Therapies	Hot flashes	Mood	Sleep	Pain	Difficulty concentrating
Hormonal	+	+	+	NM	NS
Non-hormonal pharma	+	+	+	NM	NM
Traditional East Asian Medicine	+/-	+	+	NM	NM
Mind-Body	+/-	+	+	NM	+

+=significant treatment effects, NS=nonsignificant, NM=not measured

Promising Therapies with Effects on Multiple Symptoms

- Selected Chinese herbal medicine and acupuncture therapies
- Black cohosh, especially as mixtures, and selected herbs, e.g. Rheum rhaponticum and French maritime bark
- Isoflavone therapies
- Mindfulness-based therapies
- Yoga
- Few adverse effects reported

Thank You

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Acupuncture Results

Author, Yr	Intervention/Control	HFs	Sleep	Mood	Cog.	Pain
Avis, 2008	2x/week – 8 weeks. Control (C): usual care; sham acup.	**NS***	**NS**	**NS**	**NM**	**NM**
Borud, ’09	10 tx, TCM dx, self-care. C: self-care	**+**	**+**	**NM**	**NM**	**+**
Borud, ’10	Follow up @ 6 & 12 mos.	**NS**	**NS**	**NS**	**NM**	**NS**
Huang, ’06	9 tx in 7 wks. C: off points Streitberger	**NS**	**NS**	**NS**	**NM**	**NS**
Kim, ’10	3x/wk – 4 wks. C: Usual care.	**+**	**NM**	**NS**	**NM**	**NM**
Nir, ’07	2x/wk – 7 wks. TCM dx. C: Streitberger –sham	**+**	**NM**	**NS**	**NM**	**NS**
Sunay, ’11	2x/wk– 5 wk. C: Streitberger	**+**	**NM**	**+**	**NM**	**NM**
Venzke, ’10	16 tx in 12 wks, TCM. C: off points.	**+ ***	**NM**	**NS**	**NM**	**NS**

Results table – CHM, Moxibustion

Author, Yr	Intervention/Control	HFs	Sleep	Mood	Cog.	Pain
CHM Haines'08	Dang gui bu xue tang. Control (C) : placebo pill. 6 months.	**NS**	**NM**	**NS**	**NM**	**NS**
Kwee, 2007	Zhi bai di huang +/- by dx. C: (1) placebo (2) HRT. 16 wks.	**+**	**NM**	**+**	**NM**	**NS**
Qian, 2010	Kun bao wan + Xiao yao wan; herbs + psych C: psych only. 6 mos	**+**	**+**	**+**	**NM**	**+**
Van der Sluijs, 2009	Er xian tang + zhi bai di huang wan (mod) +Black cohosh C: placebo tablets. 16 wks	**NS**	**NM**	**NS**	**NM**	**NS**
MOXA Park, '09	Moxa –book; moxa-clinical exp. C: wait list	**+**	**NM**	**+**	**NM**	**+**

Between group findings: + P<0.05 or lower NS non-significant NM Not measured

Other Herbs

Study	Intervention	Hot Flashes		Sleep		Cognitive		Mood		Pain	
		B	W	B	W	B	W	B	W	B	W
Hsu, CC, 2011	Diacorea alata	NS	+	+	+	NR	NR	+	+	NR	+
Van Die, 2009	H. perforatum L plus V. agnus-castus L	NS	+	NS	+	NR	NR	NS	+	NR	NR
Kaszkin-Bettag, 2009	Rheum rhaponticum dry extract	+	+	+	↓	NR	NR	+	↓	+	↓
Heger, 2006	Rheum rhaponticum	+	+	+	+	NR	NR	+	+	+	+
Yang, 2007	French maritime pine bark extract	+	+	+	+	+	+	+	+	NR	NR
Green, 2007	Consultations & herbal medicines	+	+	NM	NM	NR	NR	+	↓	NR	NR
Chandeying, V 2007	Pueraria mirifica 50 mg	NS	↓	NS	↓	NR	NR	NS	↓	NS	↓
Lamlertkittikul, S, 2004	50 and 100 mg Puerari mirifica	NM	NS/NS	NM	NM	NR	NR	NM	+/+	NM	-/ +
Winther et al 2005	Femal	+	+	NS	NR	NR	NR	NS	+	NS	+

Study	Intervention/Comparison	Hot Flash	Sleep	Cog-fxn	Mood	Pain
Basaria 2009	20g soy protein vs. 20g whole milk protein	NS	NM	NS	+	NM
Hanachi 2008	12.5g soy protein in soymilk vs. soymilk + walking 1 hour	?	NS	NS	NS	NS
Jou 2008	6g soy germ extract vs. roasted wheat	+	NS	NM	NS	NS
Welty 2007	25g soy protein (soy nuts) vs. TLC diet (low cholesterol)	+	NM	NM	+	NM
Lewis 2006	25g soy in soy flour muffins vs. ground flaxseed muffings vs. wheat flour muffins	NS	NM	NM	NM	NM

Results: Isoflavones

Study	Intervention/Comparison	Hot Flashes	Sleep	Cog-fxn	Mood	Pain
Evans 2011	Synthetic Genistein (30mg) vs. Placebo	+	NM	NM	NS	NM
Carmignani 2010	Isoflavone powder (90mg) vs. HT vs. placebo	+	NM	NM	+	+
Lee 2010	Rexflavone (135mg) vs. placebo	+	+	NM	NS	+
Albertazzi 2005	Genistein (90mg) vs. placebo	+ (HF>9)	NS	NM	NS	NM

Results: Isoflavones

Study	Intervention/Comparison	Hot Flashes	Sleep	Cog-fxn	Mood	Pain
Hildago 2005	Red Clover Isoflavone (80mg) vs. placebo	+	+	+	+	+
Jou 2005	70mg isoflavone vs. 35mg isoflavone vs. placebo	NS	+	NM	+	NM
Uesugi 2004	40mg isoflavone vs. placebo	NS	NS	NM	NS	NS

Key:
+ is significant for P<=0.05 or better
NS is Not Significant
NM is Not Measured

Results – Mind Body Therapies and Co-occurring Symptoms

Physical activity/exercise

Study	Intervention/comparison	Hot flash	Sleep	Cog - fxn	Mood	Pain
Huang 2010	Intensive lifestyle & behavioral change vs structured health education (wt loss/exercise)	+	-	+	-	-
Morijama 2008	Exercise + estradiol; Exercise Sedentary + estradiol; sedentary + placebo; sedentary	+	-	+	-	+
Elavasky 2007	Walking + indiv. exercise prescription Yoga Wait list	+	-	-	-	+
Wilbur 2005	Walking vs non-walking control	+	+	+	+	-
Aeillo 2004	Exercise group vs stretching control	+		+		
Lind-Strand 2004	Exercise vs unopposed estradiol	+			+	

Results – co-occurring symptoms

Relaxation Therapies

Study	Intervention/comparison	Hot flash	Sleep	Cog - fxn	Mood	Pain
Carmody 2011	MBSR vs wait list control	+	+	-	+	-
Nedstrand 2005	Applied relaxation vs unopposed estradiol	+	-	-	+	-

Yoga

Study	Intervention/comparison	Hot flash	Sleep	Cog - fxn	Mood	Pain
Chatta 2008	Integrated Yoga vs simple physical exercise	+	+	-	+	+