

Electronic Supplementary Material

Cintron D, Lipford M, Larrea Mantilla L, Spencer-Bonilla G, Lloyd R, Gionfriddo MR, Gunjal S, Farrell AM, Miller V, Murad MH. The Efficacy of Menopausal Hormone Therapy on Sleep Quality: Systematic Review and Meta-analysis.

eAppendix 1 Search Strategy October 5, 2015.

eTable 1 Summary of trial and population characteristics of eligible 42 randomized clinical trials

eTable 2 Risk of Bias of individual studies

eFig.1 Forest plot for subgroup based on risk of bias

eFig.2 Forest plot for subgroup based on intervention length

eTable 3 Classification by sleep specialists of scales with at least one sleep item into any of the applicable seven domains of sleep quality assessed by the Pittsburgh Sleep Quality Index

The supplementary material has been provided by the authors to give readers additional information about their work.

eAppendix 1. Search strategy October 5, 2015.

Database	Number of References	After de-duplication
Ovid MEDLINE	113	113
Ovid Embase	221	141
Ovid PsychInfo	125	112
Scopus	189	56
Ovid Cochrane EBM & Central	67	2
Total	--	424

MEDLINE: 113

1. menopause/ or menopause, premature/ or perimenopause/ or postmenopause/ or ((change adj life) or menopau* or perimenopau* or postmenopau* or peri-menopau* or post-menopau*).tw
2. ("Estrogens, Conjugated (USP)"/ or Estrogen Replacement Therapy/ or (estradiol* or estriol or 17-beta-estradiol or estrogen* or oestrogen or progestin or estroprogestin* or premarin or oestrogen* or climopax or carentil or oestro-feminal or estrogen-feminal or prelestrin or transannon or femavit or climarest or presomen or progens or oestrofeminal or estrofeminal or dagynil or cenestin or bazedoxifene or hydroxyestradiol or estrogel or estrema or estratab or estrapatch or estradot or divigel or Estraderm or estrace or estrasorb or estergon or oestradiol or oestrodose or oestroform or oestrogel or sandrena or vagifem or valergen or vivelle).tw
3. Exp sleep or exp sleep disorders or (Sleep* or insomnia* or dyssomnia* or parasomnia* or (early adj awake*).tw
4. 1 and 2 and 3
5. Remove duplicates from 4
6. Limit 5 to 2000
7. Limit 6 to randomized controlled trials
8. 6 and (double-blind method/ or (randomi* or blind* or mask*2).tw)
9. 7 or 8

Embase: 141

1. "menopause and climacterium"/ or climacterium/ or early menopause/ or menopause/ or postmenopause/ or ((change adj life) or menopau* or perimenopau* or postmenopau* or peri-menopau* or post-menopau*).tw
2. Exp conjugated estrogen derivative/ or exp conjugated estrogen/ or estrogen therapy/ or (estradiol* or estriol or 17-beta-estradiol or estrogen* or progestin or oestrogen or estroprogestin* or premarin or oestrogen* or climopax or carentil or oestro-feminal or estrogen-feminal or prelestrin or transannon or femavit or climarest or presomen or progens or oestrofeminal or estrofeminal or dagynil or cenestin or bazedoxifene or hydroxyestradiol or estrogel or estrema or estratab or estrapatch or estradot or divigel or Estraderm or estrace or estrasorb or estergon or oestradiol or oestrodose or oestroform or oestrogel or sandrena or vagifem or valergen or vivelle).tw
3. Exp sleep/ or exp sleep disorder/ or (Sleep* or insomnia* or dyssomnia* or parasomnia* or early adj awake*).tw
4. 1 and 2 and 3
5. Remove duplicates from 4
6. Limit 5 to 2000
7. Limit 6 to randomized controlled trials
8. 6 and (double-blind method/ or (randomi* or blind* or mask*2).tw)
9. 7 or 8

Ovid PsychInfo: 112

Database: PsycINFO<1987 to September Week 5 2015> Search Strategy:

-
1. menopause/ or ((change adj life) or menopau* or perimenopau* or postmenopau* or peri-menopau* or post-menopau*).tw.
 2. estrogens/ or estradiol/ or estrone/

3. estrogens/ or estradiol/ or estrone/ or (estradiol* or estriol or 17-beta-estradiol or estrogen* or progestin or oestrogen or estropogest* or premarin or oestrogen* or climopax or carentil or oestro-feminal or estro-feminal or prelestrin or transannon or femavit or climarest or presomen or progens or oestrofeminal or estrofeminal or dagynil or cenestin or bazedoxifene or hydroxyestradiol or estrogen or estrema or estratab or estrapatch or estradot or divigel or Estraderm or estrace or estrasorb or estergon or oestradiol or oestrodose or oestroform or oestrogen or sandrena or vagifem or valergen or vivelle).tw.
4. 1 and 2 and 3
5. remove duplicates from 4
6. limit 5 to yr="2000 - 2016"
7. 6 and (randomi* or blind* or mask*2).tw.

Scopus: 56

((TITLE-ABS-KEY (menopau* OR perimenopau* OR postmenopau* OR peri-menopau* OR post-menopau*)) AND (TITLE-ABS-KEY (estradiol* OR estriol OR 17-beta-estradiol or estrogen* OR oestrogen OR progestin OR estropogest* OR premarin OR oestrogen* OR climopax OR carentil OR oestro-feminal OR estro-feminal OR prelestrin OR transannon OR femavit OR climarest OR presomen OR progens OR oestrofeminal OR estrofeminal OR dagynil OR cenestin OR bazedoxifene OR hydroxyestradiol OR estrogen OR estrema OR estratab OR estrapatch OR estradot OR divigel OR estraderm OR estrace OR estrasorb OR estergon OR oestradiol OR oestrodose OR oestroform OR oestrogen OR sandrena OR vagifem OR valergen OR vivelle)) AND (TITLE-ABS-KEY (sleep* OR insomnia* OR dyssomnia* OR parasomnia* OR (early W/1 awake*))) AND (TITLE-ABS-KEY (randomi* OR blind* OR mask*)) AND (LIMIT-TO (PUBYEAR, 2015) OR LIMIT-TO (PUBYEAR, 2014) OR LIMIT-TO (PUBYEAR, 2013) OR LIMIT-TO (PUBYEAR, 2012) OR LIMIT-TO (PUBYEAR, 2011) OR LIMIT-TO (PUBYEAR, 2010) OR LIMIT-TO (PUBYEAR, 2009) OR LIMIT-TO (PUBYEAR, 2008) OR LIMIT-TO (PUBYEAR, 2007) OR LIMIT-TO (PUBYEAR, 2006) OR LIMIT-TO (PUBYEAR, 2005) OR LIMIT-TO (PUBYEAR, 2004) OR LIMIT-TO (PUBYEAR, 2003) OR LIMIT-TO (PUBYEAR, 2002) OR LIMIT-TO (PUBYEAR, 2001) OR LIMIT-TO (PUBYEAR, 2000))

Ovid Cochrane EBM & Central: 2

EBM Reviews - Cochrane Database of Systematic Reviews <2005 to August 2015>, EBM Reviews - ACP Journal Club <1991 to September 2015>, EBM Reviews - Database of Abstracts of Reviews of Effects <2nd Quarter 2015>, EBM Reviews - Cochrane Central Register of Controlled Trials <August 2015>, EBM Reviews - Cochrane Methodology Register <3rd Quarter 2012>, EBM Reviews - Health Technology Assessment <3rd Quarter 2015>, 2012>EBM Reviews - NHS Economic Evaluation Database <2nd Quarter 2015>

Search Strategy:

-
1. ((change adj life) or menopau* or perimenopau* or postmenopau* or peri-menopau* or post-menopau*).ti,ab. (13556)
 2. (estradiol* or estriol or 17-beta-estradiol or estrogen* or oestrogen or progestin or estropogest* or premarin or oestrogen* or climopax or carentil or oestro-feminal or estro-feminal or prelestrin or transannon or femavit or climarest or presomen or progens or oestrofeminal or estrofeminal or dagynil or cenestin or bazedoxifene or hydroxyestradiol or estrogen or estrema or estratab or estrapatch or estradot or divigel or Estraderm or estrace or estrasorb or estergon or oestradiol or oestrodose or oestroform or oestrogen or sandrena or vagifem or valergen or vivelle).ti,ab. (7469)
 3. (Sleep* or insomnia* or dyssomnia* or parasomnia* or (early adj awake*)).ti,ab. (16372)
1 and 2 and 3 (104)
 4. limit 4 to yr="2000 - 2015" [Limit not valid in DARE; records were retained] (88)
 5. remove duplicates from 5 (84)
 6. (randomi* or blind* or mask*2).ti,ab. (430705)
 7. 6 and 7 (67)

eTable 1. Summary of trial and population characteristics of eligible 42 randomized clinical trials									
Reference	Country	Comparison/ Sample Size [Acronym]	Menopause Definition	Race [n(%)]	Inclusion Criteria	Type MHT, Dose (mg/day)	Duratio n (wks)	Assessment of Sleep Quality	Reported Effect on Sleep
Barnabei et al.,2002 ¹	USA	Placebo/ 2763 [HERS]	LMP > 5 years + FSH > 40 mIU/ml Or BO	W 2451(88) B 218 (7.8) O 94 (3.4)	Coronary artery disease	o-CEE 0.625 + MDP 2.5	208	MSQ	Benefit
Shulman et al., 2002 ²	USA	Parallel/626	LMP > 12 m Or 6 m >LMP>12 m + E2<20 pg/mL+ FSH>40 mIU/mL	W 575(91) B 30 (4.8) H 22 (3.5) A 6 (0.009) O 3 (0.005)	Moderate to severe hot flushes	o-E2 0.045 + levonorgestrel 0.015	52	WHQ	Benefit, equal
						o-E2 0.045 + levonorgestrel 0.03			
						o-E2 0.045 + levonorgestrel 0.04			
Hays et al., 2003 ³	USA	Placebo/16008 [WHI]	50-54 y/o+ LMP >12 m >54 y/o + LMP >6 m	W 13945(87) B 1124 (7.0) H 888(5.5) A 363 (2.2) I 56(0.003) U 232 (1.4)		o-CEE 0.625 + MDP 2.5	156	WHIIRS	Benefit, small not clinically significant
								RAND-SF 36	NR
Gelfand et al.,2003 ⁴	Canada	Placebo/ 119	LMP > 6 m	W 115 (97) B 1(0.008) A 2 (1.7) O 1(0.008)	VMS	o-E2 1+ Norgestimate 0.09	12	KI	NR
Saletu-Zyhlarz et al., 2003 ⁵	Austria	Placebo/ 55 +	LMP > 24 m + E<55 pg/mL+ FSH>19 mIU/mL + KI >15	NR	Insomnia + VMS	o-EV 2 + dienogest 3 (Climodien)	8	PSQI	Benefit, higher Climodien
								SSA Sleep Quality	Benefit, equal
								SSA Awakening	No benefit
								SSA Somatic Complaints	No Benefit
								SSA Total Score	Benefit, higher

									Climodien
Sherman et al., 2003 ⁶	USA	Placebo/246 [ERA trial]	>55 y/o + LMP >5 years	W 208 (83)	Coronary Artery Disease	o-CEE 0.625	156	WHIIRS RAND 36	No Benefit
						o-CEE 0.625 +MPA 2.5			
Morrison et al., 2004 ⁷	USA	Placebo/ 57	LMP > 1 year with FSH >40 mIU/mL if <5 years of menopause	W 25(44) B 27 (47) H 1(1.7) O 4 (7)	Depression	t-E2 0.01 + o-MDP 10	8	WHQ	NR
Rudolph et al., 2004 ⁸	Germany	Placebo/ 129	ICD-10: N95.1	NR	Depression	o-EV 2 + dienogest 2	24	WHQ	Benefit
Schurmann et al., 2004 ⁹	Germany, Netherlands	Placebo/ 225	E < 20 pg/mL + FSH > 50 U/L	NR	>5 Moderate severe hot flushes	o-Estradiol 1 + Drospirenone 1	16	SleepDailyDiary Card	Benefit, equal
						o-Estradiol 1 + Drospirenone 2			
						o-Estradiol 1 + Drospirenone 3			
Dayal et al., 2005 ¹⁰	USA	Placebo / 50	LMP >12 m or LMP >6 m+ FSH 40 mIU/mL	NR		DHEA 50	12	WHQ	No Benefit
						o-CEE 0.625			
						o-CEE 0.625 + DHEA 50			
Drapier-Faure et al., 2005 ¹¹	France	Parallel/ 143	LMP or receiving MHT > 2 years	NR		EV 2 + Dienogest 2	52	WHQ	Benefit
						EV 2+ CA 1 (cyclical)			No Benefit
Levine et al., 2005 ¹²	USA	Parallel / 624 +	LMP >1 year + FSH > 40 mIU/mL+ E <20 pg/mL	NR		t-E2 0.05	52	WHIIRS	Benefit, equal
						t-E2 0.05 + NA 0.14			
						t-E2 0.05 + NA 0.25			
						t-E2 0.05 + NA 0.40			
		Placebo / 226 +	NR		12	WHIIRS	Benefit, equal		
						t-E2 0.05 + NA 0.25			

						t-E2 0.05 + NA 0.40			
Elfituri et al., 2005 ¹³	Libya	Parallel/100	LMP > 12 m or >3 m after BO	NR		Tibolone 2.5	52	Author Developed Menopause 10 symptoms Questionnaire	Benefit
						o-E2 2 + dydrogesterone 10			Benefit
Heinrich et al., 2005 ¹⁴	Germany	Placebo/ 51	Hysterectomy	NR	hysterecto mized	EV 2	24	ADSK Sleep item + Sleep item from Menopausal Index (combined)	No benefit
						EV 2 + mP 100			
Haines et al., 2005 ¹⁵	China, Hong Kong, Indonesia, Korea, Malaysia, Pakistan, Philippines, Singapore, Taiwan, Thailand, Vietnam	Placebo/ 1028 [PAM study]	LMP > 12 m	A 1028(100)	Menopaus al symptoms including VMS	o-CEE 0.625 + MDP 2.5	24	Sleep Daily Diary Card	Benefit, equal
						o-CEE 0.45 + MDP 1.5			
						o-CEE 0.30 + MDP 1.5			
Diem et al., 2006 ¹⁶	USA	Placebo/ 417 [ULTRA]	-	W 385(92)		t-E2 0.014	96	Six point Likert Scale	Benefit
Joffe et al., 2006 ¹⁷	USA	Placebo / 52	STRAW criteria	W 46(88) B 3(0.6) H 1(0.02) A 1(0.02) O 1(0.02)	Severe to moderate hot flushes	t-E2 0.05	12	PSQI	Benefit
Reddy et al., 2006 ¹⁸	USA	Placebo/ 60	LMP > 6 m or >12 m after BO or FSH > 30 mIU/mL	NR	Moderate to severe hot flushes	o-CEE 0.625	12	GCS	NR
Serrano et al., 2006 ¹⁹	Italy	Parallel/ 226	LMP > 6 m + FSH >40 U/L	NR		o-CEE 0.625 + MPA 10	52	MQoL	NR

						t-E2 0.05 + MPA 10			
LeBlanc et al., 2007 ²⁰	USA	Placebo/ 37	6 m >LMP < 36 m + FSH>920 IU/L	NR		EV 2 + MDP 5	8	OHSU SL Sleep Diary	No Benefit
Maki et al., 2007 ²¹	USA	Placebo/ 180 [COGENT]	LMP > 12-36 m or 6>LMP >12 m + FSH < lower limit for PMW	W 147(82) B 17(9.4) H 11(6.1) A 2(1.1)	Cognitive complaint	o-CEE 0.625 + MDP 2.5	16	PSQI	Small benefit, data not shown
								GCS	NR
Pitkin et al., 2007 ²²	Finland, Sweden, Denmark, Germany, Poland, Czech Republic, Hungary, Russia	Parallel/ 459	LMP> 12-36 m or >6 m after BO	NR	Moderate to severe hot flushes	EV 1 + MDP 2.5	52	WHQ	Benefit, equal
						EV 1 + MDP 5			
						EV 2 + MDP 5			
Hachul et al., 2008 ²³	Brazil	Placebo/ 33 +	LMP > 1 year + FSH >30 mIU/mL	NR		o-CEE 0.625 + MDP 2.5	24	KI	NR
								ESS	No benefit
Kalleinen et al., 2008 ²⁴	Finland	Placebo/ 18 +	By age and amenorrhea (no further details)	NR		EV 2 + Norethisterone 0.7	24	BNSQ	No Benefit, unfavorable
Honjo et al., 2009 ²⁵	Japan	Placebo/ 211	LMP >1 year + FSH > 30 mIU/mL , E2 <20 pg/mL or >1 m after BO	A 211(100)	Moderate to Severe Hot flushes	mE2 0.5	8	Self-report sleep scale	Benefit, greater and earlier for higher dose
						mE2 1.0			
Baksu et al., 2009 ²⁶	Turkey	No treatment / 132	Surgically menopausal	NR		o-CEE 0.625	52	KI	Benefit
Padua et al., 2010 ²⁷	Brazil	Placebo/ 50	LMP > 12 m + FSH >35 IU/L	H 50 (100)	Chronic Hepatitis C	t-E2 0.05 + o- NA 0.17	36	KI	No Benefit

Joffe et al., 2011 ²⁸	USA	Placebo/ 41 +	STRAW criteria	W 26(63) B 13(32) O 2(0.05)	Unipolar depression + insomnia	t-E2 0.5	8	PSQI	NR
Lin et al., 2011 ²⁹	China	Placebo/ 244	LMP > 1 year or >6 wks after BO or LMP > 6 m + FSH >40 mIU/mL	A 244(100)	Moderate to severe VMS	o-E2 1 + Drospirenone 2	18	Symptom Diary Cards	No Benefit
Sanchez-Rodriguez et al., 2013 ³⁰	Mexico	Placebo/ 111	-	H 111(100)		o-CEE 0.625 + MPA 5	24	WHOQoL, Brief	NR
Polisseni et al., 2013 ³¹	Brazil	Parallel/ 86	-	W 48(56) O 38(44)	Moderate to severe hot flushes	o- Tiboline 2.5 o-oestradiol 1 + NA 0.5	12	WHQ	Benefit, equal
Caglayan et al., 2014 ³²	Turkey	Parallel/ 73	-	NR		EV 2 + Dienogest 2 EV 2 + Dienogest 10	24	KI	NR
Abraham et al., 2014 ^{33*}	USA	Placebo/ 3544 [SMART 1]	LMP ≥12 +FSH > 30 mIU /mL+E<183 pmol/L	W 2878 (81) B 482(13.6) H 135 (3.8) O 25 (0.7)		o-CEE 0.45 +BZA 10	104	MQoL Sleep diary	NR
						o-CEE 0.45 +BZA 20			Benefit, irrespective of years from menopause
						o-CEE 0.45+BZA 40			NR
						o-CEE 0.625+BZA 10			NR
						o-CEE 0.625+BZA 20			Benefit, irrespective of years from menopause

						o-CEE 0.625+BZA 40			NR
		Placebo/332 [SMART 2]	LMP \geq 12 m or LMP>6 m + FSH>40 mIU/mL	W 271(85) B 34(11) H 18(5.6) O 10 (3.1)	Severe hot flushes	o-CEE 0.45+BZA 20 o-CEE 0.625+BZA 20	12	MQoL MOS	Benefit, equal irrespective of years from menopause
		Placebo/575 [SMART 3]		W 496(86) B 19(3.3) H 33(5.7) O 27(4.7)	Vulvar vaginal atrophy moderate to severe symptoms	o-CEE 0.45+BZA 20 o-CEE 0.625+BZA 20	12	MQoL	NR
		Placebo/1613 [SMART 5]		W 1451(89) B 109(6.7) O 53(3.3)		o-CEE 0.45+BZA 20 o-CEE 0.625+BZA 20 o-CEE 0.45 +MPA 1.5	52	MOS MQoL	Benefit in subgroup VMS+ sleep problems
Savolainen- Peltonen et al., 2014 ³⁴	Finland	Placebo/ 107	6 m > LMP>36 m+ FSH>30 U/L	NR	½ women with severe VMS, ½ symptom free	o- E2 2 o-E2 2+ MPA 5	24	WHQ	Benefit, for women with VMS No benefit for women without VMS
Toffol et al., 2014 ³⁵	Finland	Placebo / 18	\geq 58 y/ o + LMP > 1 year	NR		o-EV 2 + NA 0.07	24	BNSQ Preceding night sleep score	NR
Ensrud et al., 2015 ³⁶	USA	Placebo/ 243 [MsFLASH]	LMP \geq 60 days LMP \geq 12 m or BO Or FSH >20 mIU/mL + E \leq 50 pg/mL	W 150(62) B 78(32) O 15(6.2)	Severe VMS	o-E2 0.5	8	PSQI	Modest Benefit
Kling et al., 2015 ³⁷	USA	Placebo/ 95 [KEEPS]	6 m >LMP < 36 m + FSH	NR		o-CEE 0.45 + P 200	192	MSQ	No Benefit

			≥ 35 mIU/mL + E <40 pg/mL			t-E2 0.05 + P 200			
Tansupwatdiku l et al., 2015 ³⁸	Thailand	Placebo/ 40 +	LMP > 1 year or BO	NR	insomnia	t-E2 0.005	8	ISI ESS	No benefit

Summary of eligible 42 randomized clinical trials organized by year of publication.* For SMART trials data extraction, a total of 16 publications were found, given multiple reports for a single trial. Abbreviations: BO= bilateral oophorectomy ; +: Primary outcome was sleep quality or insomnia ; NR: Not reported; W, white; B, black; H, Hispanic; A, Asian; I, Native Indian; O, other; U, unclear or unknown; MQoL: Menopause Quality of Life Questionnaire, MOS: Medical Outcomes Sleep Scale, KI: Kupperman Index; MSQ: Menopausal Symptom Questionnaire; WHIIRS: Women’s Health Initiative Insomnia Rating Scale; RAND-SF 36: RAND Short Form 36 Item Health Survey; PSQI: Pittsburgh Sleep Quality Index ; ESS: Epworth Sleepiness Scale; ADS-K: German version of Center for Epidemiological Studies Depression Scale, authors used only sleep item for sleep quality assessment; BNSQ : Basic Nordic Sleep Questionnaire ; OHSU SL: Oregon Health and Science University Sleep Laboratory ; GCS: Green Climacteric Scale; WHQ : Women’s Health Questionnaire; SSA: Self-Assessment of Sleep and Awakening Quality Scale; WHOQoL: World Health Organization Quality of Life Brief Questionnaire; ISI: Insomnia Severity Index; CEE: conjugated equine estrogen; BZA: bazedoxifene; MPA : medroxyprogesterone acetate; EV: estradiol valerate ; DHEA: Dehydroepiandrosterone; E2:17 beta estradiol; CA : Crypterone Acetate; mP: micronized-progesterone; mE2:micronized 17b beta estradiol ; P: Progesterone; NA: Norethidrone Acetate; L: levonorgestrel; PMW : post-menopausal women.

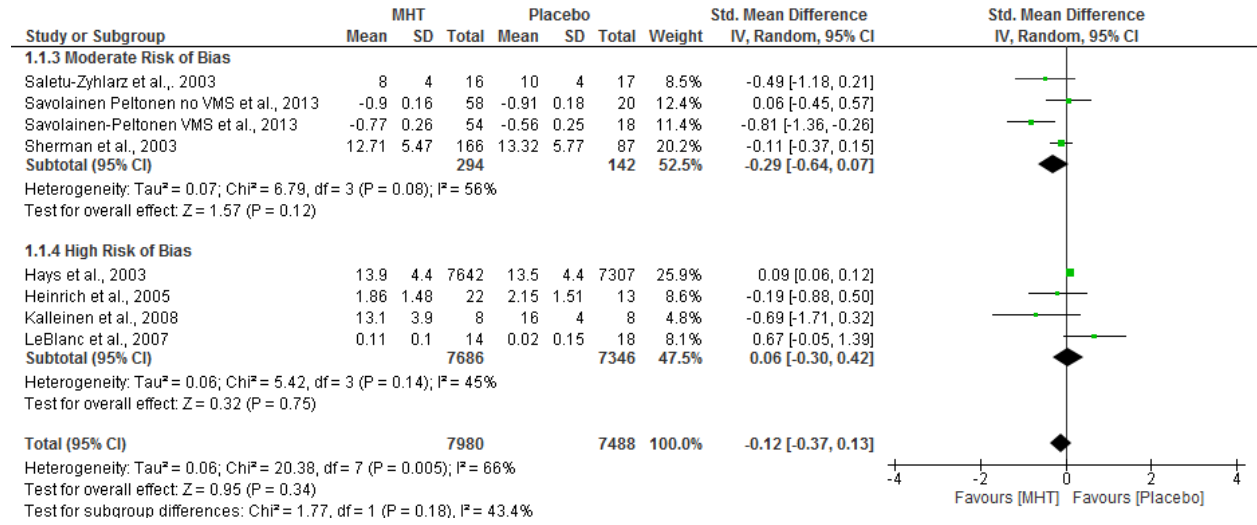
eTable 2. Cochrane Risk of Bias Quality Assessment

Reference	SG	AC	BP	BOA	IOD	SOR	Other	Overall
Barnabei et al,2002	Low	Low	Low	Low	Low	Unclear	High	Mod
Schulman et al., 2002	Low	Low	High	Low	Low	Unclear	Unclear	High
Hays et al., 2003	Unclear	High	Low	Unclear	Unclear	Unclear	High	High
Gelfand et al.,2013	Low	Low	Low	Unclear	High	Unclear	High	Mod
Saletu-Zyhlarz et al., 2003	Unclear	Unclear	Low	Unclear	Unclear	Unclear	High	Mod
Sherman et al., 2003	Low	Unclear	Low	Low	Unclear	Low	Unclear	Mod
Morrison et al., 2004	Low	Unclear	High	High	Low	High	Low	High
Rudolph et al., 2004	Low	Low	Low	Unclear	High	Unclear	High	Mod
Schurmann et al., 2004	Low	Unclear	Low	Unclear	Low	Unclear	High	High
Dayal et al., 2005	Low	Unclear	Unclear	Unclear	Low	Unclear	Unclear	High
Drapier-Faure et al., 2005	Unclear	Unclear	High	Unclear	High	Unclear	Unclear	High
Levine et al., 2005	Unclear	Unclear	Low	Unclear	Low	Low	Unclear	Mod
Elfituri et al., 2005	Unclear	Unclear	Unclear	Unclear	Low	Unclear	Unclear	Mod
Heinrich et al., 2005	Unclear	Unclear	Unclear	Unclear	High	Unclear	Unclear	High
Haines et al., 2005	Unclear	Unclear	Unclear	Unclear	High	Unclear	High	High
Diem et al., 2006	Low	Unclear	Low	Low	Low	Unclear	High	Mod
Joffe et al., 2006	Unclear	Unclear	Low	Unclear	Low	High	Low	Mod
Reddy et al., 2006	Low	Unclear	Low	Unclear	Low	Low	High	Mod
Serrano et al., 2006	Low	Low	High	Low	Low	Unclear	Unclear	High
LeBlanc et al., 2007	High	Unclear	Low	Unclear	Low	Unclear	High	High
Maki et al., 2007	Low	Unclear	Unclear	Unclear	High	Unclear	High	High
Pitkin et al., 2007	Unclear	Unclear	Low	Unclear	Low	High	High	Mod
Hachul et al., 2008	Unclear	Unclear	Low	Unclear	Low	Unclear	Low	Mod
Kalleinen et al., 2008	Low	Low	Unclear	Low	Low	Unclear	High	High
Honjo et al., 2009	Low	Unclear	Unclear	Unclear	Low	Unclear	High	High
Baksu et al., 2009	Low	Low	Low	Low	Low	Unclear	Unclear	Mod
Padua et al., 2010	Low	Unclear	Unclear	Unclear	Low	Unclear	Unclear	High
Joffe et al., 2011	Unclear	Unclear	Low	Unclear	Low	Unclear	High	Mod
Lin et al., 2011	Low	Unclear	Low	Unclear	Low	High	Unclear	Mod
Sanchez-Rodriguez et al., 2013	Low	Unclear	Unclear	Unclear	High	Unclear	Unclear	Mod
Polisseni et al., 2013	Unclear	Unclear	Low	Unclear	Low	Unclear	Low	Mod
Caglayan et al., 2014	Unclear	Unclear	Unclear	Unclear	Unclear	Unclear	Unclear	High
Abraham et al., 2014	Low	Unclear	Unclear	Unclear	Low	High	High	High
Savolainen-Peltonen et al., 2014	Low	Low	Low	Unclear	Low	Unclear	Low	Mod
Toffol et al., 2014	Low	Low	Low	Low	Low	Low	High	Mod

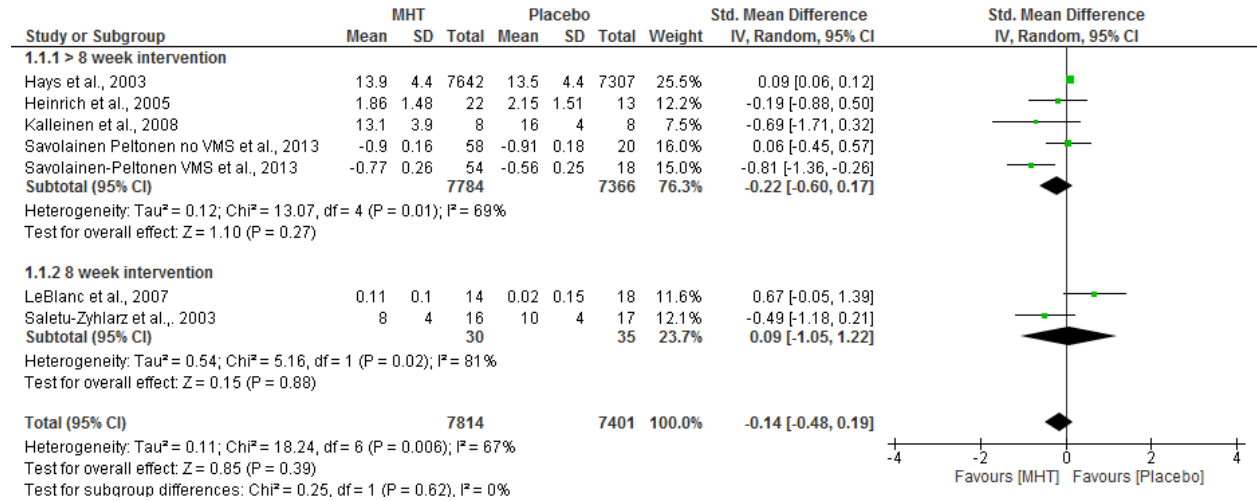
Ensrud et al., 2015	Low	Unclear	Low	Unclear	Low	Low	Low	Mod
Kling et al., 2015	Low	Unclear	Low	Unclear	Low	Unclear	High	Mod
Tansupwatdikul et al., 2015	Low	Low	Low	Low	Low	Low	Low	Low

Quality Assessment results from Cochrane Risk of Bias Tool. Abbreviations- SG: Sequence Generation, AC: Allocation Concealment, BP: Blinding of Participants, BOA: Blinding of Outcome Assessors, IOD: Incomplete Outcome Data, SOR : Selective Outcome Reporting.

eFig1. Standardized mean differences subgroup analyses based on risk of bias characteristic with moderate risk trials compared to high risk.



eFig 2. Standardized mean differences subgroup analyses based on length of intervention characteristics with trials with interventions longer than 8 weeks compared to 8 week trials



eTable3. Classification by sleep specialists of scales with at least one sleep item into any of the applicable seven domains of sleep quality assessed by the Pittsburgh Sleep Quality Index

Scale	SQ	SL	SD	HSE	SD	DD	MU
PSQI	x	x	x	x	x	x	x
Menopause Specific Quality of Life Questionnaire					x	x	
KI		x			x	x	
Menopausal Symptom 6 item Likert Scale		x			x	x	
WHQ		x		x	x	x	
Daily Symptom Rating Calendar					x	x	
6 point likert scale				x	x	x	
Selected Symptom List and scored like Green Climacteric		x			x	x	
ISI	x	x		x		x	
Menopause Quality of Life Questionnaire				x	x	x	
ESS						x	
UNIFESP Sleep Questionnaire		x			x		
Daily Diary cards		x			x	x	
WHIIRS	x	x		x	x		
CES-D Sleep item (included in sleep quality assessment)		x					
Patient Questionnaire		x			x	x	
BNSQ	x	x	x	x	x	x	x
Menopausal Symptom Questionnaire		x			x	x	
GCS		x			x	x	
Symptom Diary cards	x					x	
UQoL Scale						x	
RAND 36						x	
15-D Quality of Life Questionnaire	x					x	

Visual Analogue Scale					x	x
100 mm visual analogue scale	x					x
Daily diary cards	x					x
Medical Outcomes Sleep Scale		x	x	x	x	x
WHO-QoL BREF	x				x	x
Elfituri Independently developed Menopausal Symptom Questionnaire				x	x	
Preceding Night Sleep Questionnaire	n/a					
OHSU SL Sleep Diary	n/a					
SSA	n/a					

Abbreviations- SQ, Sleep quality; SL, Sleep latency; SD, Sleep Duration; HSE, Habitual Sleep Efficiency; SD, Sleep Disturbances; DD, Daytime Dysfunction; MU, Medication Use.

Supplement References:

1. Barnabei VM, Grady D, Stovall DW, et al. Menopausal symptoms in older women and the effects of treatment with hormone therapy. *Obstet Gynecol* 2002;100:1209-18.
2. Shulman LP, Yankov V, Uhl K. Safety and efficacy of a continuous once-a-week 17beta-estradiol/levonorgestrel transdermal system and its effects on vasomotor symptoms and endometrial safety in postmenopausal women: the results of two multicenter, double-blind, randomized, controlled trials. *Menopause* 2002;9:195-207.
3. Hays J, Ockene JK, Brunner RL, et al. Effects of estrogen plus progestin on health-related quality of life. *N Engl J Med* 2003;348:1839-54.
4. Gelfand MM, Moreau M, Ayotte NJ, Hilditch JR, Wong BA, Lau CY. Clinical assessment and quality of life of postmenopausal women treated with a new intermittent progestogen combination hormone replacement therapy: a placebo-controlled study. *Menopause* 2003;10:29-36.
5. Saletu-Zyhlarz G, Anderer P, Gruber G, et al. Insomnia related to postmenopausal syndrome and hormone replacement therapy: sleep laboratory studies on baseline differences between patients and controls and double-blind, placebo-controlled investigations on the effects of a novel estrogen-progestogen combination (Climodien, Lafamme) versus estrogen alone. *J Sleep Res* 2003;12:239-54.
6. Sherman AM, Shumaker SA, Sharp P, et al. No effect of HRT on health-related quality of life in postmenopausal women with heart disease. *Minerva Ginecol* 2003;55:511-7.
7. Morrison MF, Kallan MJ, Ten Have T, Katz I, Tweedy K, Battistini M. Lack of efficacy of estradiol for depression in postmenopausal women: a randomized, controlled trial. *Biol Psychiatry* 2004;55:406-12.
8. Rudolph I, Palombo-Kinne E, Kirsch B, Mellinger U, Breitbarth H, Graser T. Influence of a continuous combined HRT (2 mg estradiol valerate and 2 mg dienogest) on postmenopausal depression. *Climacteric* 2004;7:301-11.
9. Schurmann R, Holler T, Benda N. Estradiol and drospirenone for climacteric symptoms in postmenopausal women: a double-blind, randomized, placebo-controlled study of the safety and efficacy of three dose regimens. *Climacteric* 2004;7:189-96.
10. Dayal M, Sammel MD, Zhao J, Hummel AC, Vandenbourn K, Barnhart KT. Supplementation with DHEA: effect on muscle size, strength, quality of life, and lipids. *J Womens Health (Larchmt)* 2005;14:391-400.
11. Drapier-Faure E, Azoulay C, Abramovici Y. [Acceptability of continuous combined versus cyclical HRT: a French multicentric randomized clinical study]. *Gynecol Obstet Fertil* 2005;33:498-504.
12. Levine DW, Dailey ME, Rockhill B, Tipping D, Naughton MJ, Shumaker SA. Validation of the Women's Health Initiative Insomnia Rating Scale in a multicenter controlled clinical trial. *Psychosom Med* 2005;67:98-104.
13. Elfitori A, Sherif F, Elmahaishi M, Chrystyn H. Two hormone replacement therapy (HRT) regimens for middle-eastern postmenopausal women. *Maturitas* 2005;52:52-9.
14. Heinrich AB, Wolf OT. Investigating the effects of estradiol or estradiol/progesterone treatment on mood, depressive symptoms, menopausal symptoms and subjective sleep quality in older healthy hysterectomized women: a questionnaire study. *Neuropsychobiology* 2005;52:17-23.
15. Haines CJ, Xing SM, Park KH, Holinka CF, Ausmanas MK. Prevalence of menopausal symptoms in different ethnic groups of Asian women and responsiveness to therapy with three doses of conjugated estrogens/medroxyprogesterone acetate: the Pan-Asia Menopause (PAM) study. *Maturitas* 2005;52:264-76.
16. Diem S, Grady D, Quan J, et al. Effects of ultralow-dose transdermal estradiol on postmenopausal symptoms in women aged 60 to 80 years. *Menopause* 2006;13:130-8.
17. Joffe H, Hall JE, Gruber S, et al. Estrogen therapy selectively enhances prefrontal cognitive processes: a randomized, double-blind, placebo-controlled study with functional magnetic resonance imaging in perimenopausal and recently postmenopausal women. *Menopause* 2006;13:411-22.
18. Reddy SY, Warner H, Guttuso T, Jr., et al. Gabapentin, estrogen, and placebo for treating hot flashes: a randomized controlled trial. *Obstet Gynecol* 2006;108:41-8.
19. Serrano D, Mariani L, Mora S, et al. Quality of life assessment in a chemoprevention trial: fenretinide and oral or transdermal HRT. *Maturitas* 2006;55:69-75.
20. LeBlanc ES, Neiss MB, Carello PE, Samuels MH, Janowsky JS. Hot flashes and estrogen therapy do not influence cognition in early menopausal women. *Menopause* 2007;14:191-202.
21. Maki PM, Gast MJ, Vieweg AJ, Burriss SW, Yaffe K. Hormone therapy in menopausal women with cognitive complaints: a randomized, double-blind trial. *Neurology* 2007;69:1322-30.

22. Pitkin J, Smetnik VP, Vadasz P, Mustonen M, Salminen K, Ylikangas S. Continuous combined hormone replacement therapy relieves climacteric symptoms and improves health-related quality of life in early postmenopausal women. *Menopause Int* 2007;13:116-23.
23. Hachul H, Bittencourt LR, Andersen ML, Haidar MA, Baracat EC, Tufik S. Effects of hormone therapy with estrogen and/or progesterone on sleep pattern in postmenopausal women. *Int J Gynaecol Obstet* 2008;103:207-12.
24. Kalleinen N, Polo O, Himanen SL, Joutsen A, Polo-Kantola P. The effect of estrogen plus progestin treatment on sleep: a randomized, placebo-controlled, double-blind trial in premenopausal and late postmenopausal women. *Climacteric* 2008;11:233-43.
25. Honjo H, Taketani Y. Low-dose estradiol for climacteric symptoms in Japanese women: a randomized, controlled trial. *Climacteric* 2009;12:319-28.
26. Baksu B, Baksu A, Goker N, Citak S. Do different delivery systems of hormone therapy have different effects on psychological symptoms in surgically menopausal women? A randomized controlled trial. *Maturitas* 2009;62:140-5.
27. Padua MA, Fonseca AM, Deguti MM, et al. Hormone therapy in Brazilian postmenopausal women with chronic hepatitis C: a pilot study. *Climacteric* 2010;13:179-86.
28. Joffe H, Petrillo LF, Koukopoulos A, et al. Increased estradiol and improved sleep, but not hot flashes, predict enhanced mood during the menopausal transition. *J Clin Endocrinol Metab* 2011;96:E1044-54.
29. Lin SQ, Sun LZ, Lin JF, et al. Estradiol 1 mg and drospirenone 2 mg as hormone replacement therapy in postmenopausal Chinese women. *Climacteric* 2011;14:472-81.
30. Sanchez Rodriguez MA, Zacarias Flores M, Arronte Rosales A, Mendoza Nunez VM. [Effect of hormone therapy with estrogens on oxidative stress and quality of life in postmenopausal women]. *Ginecol Obstet Mex* 2013;81:11-22.
31. Polisseni AF, Andrade AT, Ribeiro LC, et al. Effects of a continuous-combined regimen of low-dose hormone therapy (oestradiol and norethindrone acetate) and tibolone on the quality of life in symptomatic postmenopausal women: a double-blind, randomised study. *Maturitas* 2013;74:172-8.
32. Caglayan EK, Kara M, Etiz S, Kumru P, Aka N, Kose G. The effects of progesterone selection on psychological symptoms in hormone replacement therapy. *Adv Clin Exp Med* 2014;23:63-7.
33. Abraham L, Pinkerton JV, Messig M, Ryan KA, Komm BS, Mirkin S. Menopause-specific quality of life across varying menopausal populations with conjugated estrogens/bazedoxifene. *Maturitas* 2014;78:212-8.
34. Savolainen-Peltonen H, Hautamaki H, Tuomikoski P, Ylikorkala O, Mikkola TS. Health-related quality of life in women with or without hot flashes: a randomized placebo-controlled trial with hormone therapy. *Menopause* 2014;21:732-9.
35. Toffol E, Kalleinen N, Haukka J, Vakkuri O, Partonen T, Polo-Kantola P. The effect of hormone therapy on serum melatonin concentrations in premenopausal and postmenopausal women: a randomized, double-blind, placebo-controlled study. *Maturitas* 2014;77:361-9.
36. Ensrud KE, Guthrie KA, Hohensee C, et al. Effects of estradiol and venlafaxine on insomnia symptoms and sleep quality in women with hot flashes. *Sleep* 2015;38:97-108.
37. Kling JM, Lahr BA, Bailey KR, Harman SM, Miller VM, Mulvagh SL. Endothelial function in women of the Kronos Early Estrogen Prevention Study. *Climacteric* 2015;18:187-97.
38. Tansupwatdikul P, Chaikittisilpa S, Jaimchariyatam N, Panyakhamlerd K, Jaisamrarn U, Taechakraichana N. Effects of estrogen therapy on postmenopausal sleep quality regardless of vasomotor symptoms: a randomized trial. *Climacteric* 2015;18:198-204.