

Appendix 1: Medline Search Strategy

- 1 exp Breast Neoplasms/
- 2 ((breast* or mamma or mammar*) adj3 (cancer* or carcinoid* or carcinoma* or carcinogen* or adenocarcinoma* or adeno-carcinoma* or malignan* or neoplasia* or neoplasm* or sarcoma* or tumour* or tumor*)).tw,kw.
- 3 exp Prostatic Neoplasms/
- 4 ((prostate or prostatic) adj3 (cancer* or carcinoid* or carcinoma* or carcinogen* or adenocarcinoma* or adeno-carcinoma* or malignan* or neoplasia* or neoplasm* or sarcoma* or tumour* or tumor*)).tw,kw.
- 5 or/1-4
- 6 Hot Flashes/
- 7 (hot flash* or hot flush*).tw,kw.
- 8 night sweat*.tw,kw.
- 9 ((vasomotor or vaso-motor) adj5 (disorder* or disturbance* or instabilit* or symptom*)).tw,kw.
- 10 ((climacteri* or menopaus* or premenopaus* or pre-menopaus* or postmenopaus* or postmenopaus*) adj5 (disorder* or disturbance* or instabilit* or symptom*)).tw,kw.
- 11 or/6-10
- 12 5 and 11
- 13 (controlled clinical trial or randomized controlled trial).pt.
- 14 clinical trials as topic.sh.
- 15 (randomi#ed or randomly or RCT\$1 or placebo*).tw.
- 16 ((singl* or doubl* or trebl* or tripl*) adj (mask* or blind* or dumm*)).tw.
- 17 trial.ti.
- 18 or/13-17
- 19 12 and 18
- 20 exp Animals/ not (exp Animals/ and Humans/)
- 21 19 not 20
- 22 (comment or editorial or interview or news).pt.
- 23 (letter not (letter and randomized controlled trial)).pt.
- 24 21 not (22 or 23)
- 25 24 use prmz [MEDLINE]
- 26 exp breast tumor/
- 27 ((breast* or mamma or mammar*) adj3 (cancer* or carcinoid* or carcinoma* or carcinogen* or adenocarcinoma* or adeno-carcinoma* or malignan* or neoplasia* or neoplasm* or sarcoma* or tumour* or tumor*)).tw,kw.
- 28 exp prostate tumor/
- 29 ((prostate or prostatic) adj3 (cancer* or carcinoid* or carcinoma* or carcinogen* or adenocarcinoma* or adeno-carcinoma* or malignan* or neoplasia* or neoplasm* or sarcoma* or tumour* or tumor*)).tw,kw.
- 30 or/26-29
- 31 hot flush/
- 32 (hot flash* or hot flush*).tw,kw.
- 33 night sweat*.tw,kw.
- 34 vasomotor disorder/
- 35 ((vasomotor or vaso-motor) adj5 (disorder* or disturb* or instabilit* or symptom*)).tw,kw.

36 ((climacteri* or menopaus* or premenopaus* or pre-menopaus* or postmenopaus* or post-
 menopaus*) adj5 (disorder* or disturb* or instabilit* or symptom*)).tw,kw.
 37 or/31-36
 38 30 and 37
 39 randomized controlled trial/ or controlled clinical trial/
 40 exp "clinical trial (topic)"/
 41 (randomi#ed or randomly or RCT\$1 or placebo*).tw.
 42 ((singl* or doubl* or trebl* or tripl*) adj (mask* or blind* or dumm*)).tw.
 43 trial.ti.
 44 or/39-43
 45 38 and 44
 46 exp animal experimentation/ or exp models animal/ or exp animal experiment/ or
 nonhuman/ or exp vertebrate/
 47 exp humans/ or exp human experimentation/ or exp human experiment/
 48 46 not 47
 49 45 not 48
 50 editorial.pt.
 51 letter.pt. not (letter.pt. and randomized controlled trial/)
 52 49 not (50 or 51)
 53 52 use emczd [EMBASE]
 54 exp Breast Neoplasms/
 55 ((breast* or mamma or mammar*) adj3 (cancer* or carcinoid* or carcinoma* or
 carcinogen* or adenocarcinoma* or adeno-carcinoma* or malignan* or neoplasia* or neoplasm*
 or sarcoma* or tumour* or tumor*)).tw.
 56 exp Prostatic Neoplasms/
 57 ((prostate or prostatic) adj3 (cancer* or carcinoid* or carcinoma* or carcinogen* or
 adenocarcinoma* or adeno-carcinoma* or malignan* or neoplasia* or neoplasm* or sarcoma* or
 tumour* or tumor*)).tw.
 58 or/54-57
 59 Hot Flashes/
 60 (hot flash* or hot flush*).tw,kw.
 61 night sweat*.tw.
 62 ((vasomotor or vaso-motor) adj5 (disorder* or disturbance* or instabilit* or
 symptom*)).tw.
 63 ((climacteri* or menopaus* or premenopaus* or pre-menopaus* or postmenopaus* or post-
 menopaus*) adj5 (disorder* or disturbance* or instabilit* or symptom*)).tw.
 64 or/59-63
 65 58 and 64
 66 (controlled clinical trial or randomized controlled trial).pt.
 67 exp Clinical Trials/
 68 (randomi#ed or randomly or RCT\$1 or placebo*).tw.
 69 ((singl* or doubl* or trebl* or tripl*) adj (mask* or blind* or dumm*)).tw.
 70 trial.ti.
 71 or/66-70
 72 65 and 71
 73 exp Animals/ not (exp Animals/ and Humans/)

- 74 72 not 73
75 (comment or editorial or interview or news).pt.
76 (letter not (letter and randomized controlled trial)).pt.
77 74 not (75 or 76)
78 77 use amed [AMED]
79 breast neoplasms/
80 ((breast* or mamma or mammar*) adj3 (cancer* or carcinoid* or carcinoma* or carcinogen* or adenocarcinoma* or adeno-carcinoma* or malignan* or neoplasia* or neoplasm* or sarcoma* or tumour* or tumor*)).tw.
81 Prostate/ and exp Neoplasms/
82 ((prostate or prostatic) adj3 (cancer* or carcinoid* or carcinoma* or carcinogen* or adenocarcinoma* or adeno-carcinoma* or malignan* or neoplasia* or neoplasm* or sarcoma* or tumour* or tumor*)).tw.
83 or/79-82
84 (hot flash* or hot flush*).tw,kw.
85 night sweat*.tw.
86 ((vasomotor or vaso-motor) adj5 (disorder* or disturb* or instabilit* or symptom*)).tw,kw.
87 ((climacteri* or menopaus* or premenopaus* or pre-menopaus* or postmenopaus* or postmenopaus*) adj5 (disorder* or disturb* or instabilit* or symptom*)).tw,kw.
88 or/84-87
89 83 and 88
90 clinical trials/
91 (randomi#ed or randomly or RCT\$1 or placebo*).tw.
92 ((singl* or doubl* or trebl* or tripl*) adj (mask* or blind* or dumm*)).tw.
93 trial.ti.
94 or/90-93
95 89 and 94
96 exp Animals/ not (exp Animals/ and Humans/)
97 95 not 96
98 97 use prmz
99 97 use emezd
100 97 use amed
101 97 not (98 or 99 or 100) [PSYCINFO]
102 25 or 53 or 78 or 101
103 remove duplicates from 102 [UNIQUE RECORDS]
104 103 use prmz [MEDLINE UNIQUE RECORDS]
105 103 use emezd [EMBASE UNIQUE RECORDS]
106 103 use amed [AMED UNIQUE RECORDS]
107 103 not (104 or 105 or 106) [PSYCINFO UNIQUE RECORDS]

Appendix 2: Overview of Study Selection Criteria

Selection criteria were originally described in the published protocol for this review. A summary of these criteria is provided in the table below.

Criteria	Description of Eligibility
Population	Studies that enrolled patients with a history of breast or prostate cancer who are experiencing hot flashes. No restrictions on age or cancer stage were employed.
Intervention and Comparators	Studies assessing non-hormonal pharmacologic, behavioral/physical, and natural health product interventions were of interest. Pharmacologic interventions of interest included anti-depressants from the selective serotonin reuptake inhibitors class (including sertraline, escitalopram, citalopram, etc) and from the selective norepinephrine reuptake inhibitor class (including duloxetine, venlafaxine, etc), and certain neuroleptic agents (gabapentin, clonidine) and anti-hypertensive medications. All doses and formulations were considered to be eligible. Physical and behavioral interventions of interest consisted of yoga, exercise programs, hypnosis, acupuncture, relaxation approaches, and cognitive behavioral therapy. Nutritional healthcare products of interest consisted of ginseng, black cohosh, flax, isoflavones, menherba, soy and vitamin E. Placebo (and other representations of inactive treatment) were also considered of interest as key sources of indirect evidence.
Outcomes	Changes in the severity and frequency of hot flashes were of primary interest. Changes in quality of life (both overall and for specific symptoms) were also of interest. The reporting format of frequency of hot flashes was known prior to starting the review to be variable amongst trials (e.g. % change from baseline, mean number per day, % of patients remaining free of hot flashes during the study); all formats were sought during data collection. Data from all validated symptom-specific and generic quality of life (QoL) scales (and their different forms of reporting) were also of interest. Secondary outcomes included measures related to adherence to cancer therapies and harms associated with each treatment (e.g., adverse drug effects, discontinuation from the study, etc).
Study Design	Randomized controlled trials were sought, with both parallel group and crossover designs being of interest. For crossover trials, data from the initial study period was considered a priori to be of focus in order to avoid bias from carryover.

Appendix 3: Additional Details, Statistical Methods for NMA

For two outcomes with enough data for NMA (hot flash score and frequency), and several included studies reported medians and interquartile ranges (IQR) as opposed to means and with standard deviations (SD), standard errors (SE) or confidence intervals (CI). Medians and related IQRs were converted to means and SDs according to methods described elsewhere by Wan et al 2014.(Wan et al., 2014) About half of the included studies reported percentage change from baseline and the other half reported the absolute values. We transformed absolute/percentage changes from baseline into the difference of log mean changes from baseline across two arms and the corresponding SEs, such that the percentages were cancelled out during pre-processing:

$$\delta_{t_{i1},t_{ik}} = \ln(y_{ik}) - \ln(y_{i1}) = \ln(y_{ik}/y_{i1}), \quad k > 1,$$
$$SE\{\delta_{t_{i1},t_{ik}}\} = SE\{\ln(y_{ik}) - \ln(y_{i1})\} = \sqrt{\{SE(y_{i1})/y_{i1}\}^2 + \{SE(y_{ik})/y_{ik}\}^2}$$

where y_{i1} and y_{ik} are the absolute/percentage mean change from baseline in the 1st and k th arm of the i th study, $SE(y_{i1})$ and $SE(y_{ik})$ are the corresponding standard errors.

A contrast-based NMA model on the difference of log mean changes from baseline across two arms and the corresponding SEs following transformation was used. Both fixed effects (FE) and random effects (RE) models with Normal likelihood and the identity link were fit to the data.(Dias et al., 2011) As such, the mean difference of two interventions in the log scale can be interpreted as the log ratio of means (log RoM); when transformed back to the natural scale, estimates can be interpreted as the RoM of two interventions. We present comparisons between interventions in terms of ratios of means (RoM) with 95% credible intervals (CrI).

The probability of each intervention to be the best (referred to from here on as ‘P(best)’), the corresponding surface under the cumulative ranking curve (SUCRA) values, and the mean rank of each intervention (with 2.5% and 97.5% quantiles) were also estimated.(Salanti et al., 2011) P(best) and SUCRA values range between 0 and 1, with values nearer 1 indicative of preferred treatments. Smaller values of the mean rank also suggest preferred treatments. Further details regarding the methods and implementation of NMA are provided in the supplementary materials.

R2OpenBUGS Code Modified for Ratio of Means Network Meta-Analysis (Contrast-based)

Part A. Contrast-based random effects consistency model, modified for ratio of means analysis

```
#=====
# Set up data for R2OpenBUGS
# Pre-processing of data specifically for ratio of means NMA modeling
#=====

setwd("C:\\Hot Flash\\HF freq\\Doses combined\\RE\\")
WD <- getwd()

# A total of 100,000 iterations, among which half were burn-in
NITER = 100000
NBURNIN = 50000

# LOAD DATA
# read in study-by-treatment data
data1 = read.csv("C:\\Hot Flash\\HF freq\\Doses
combined\\study_data_incl_percent.csv", header=TRUE)

data2 = read.csv("C:\\Hot Flash\\HF freq\\Doses
combined\\treatments_incl_percent.txt", header=TRUE, sep="\t")
treatment = data2[,1]
txNames = data2[,2]
txColors = matrix(data2[,3])

# Required R package needed to call OpenBUGS
library(R2OpenBUGS)

maxnarms <- max(data1$na)
nt = length(txNames) # or, = max(treatment)
na = data1$na
ns2 = sum(na==2)
ns3 = sum(na==3)
ns4 = sum(na==4)
ns = ns2+ns3+ns4

t = matrix(NA, ns, maxnarms)
t[,1] = data1$t1
t[,2] = data1$t2
t[,3] = data1$t3
t[,4] = data1$t4

y = matrix(NA, ns, maxnarms)
y[,2] = log(data1$y2)-log(data1$y1)
y[,3] = log(data1$y3)-log(data1$y1)
y[,4] = log(data1$y4)-log(data1$y1)

sesq = matrix(NA, ns, maxnarms)
sesq[,2] = (data1$se2/data1$y2)^2 + (data1$se1/data1$y1)^2
sesq[,3] = (data1$se3/data1$y3)^2 + (data1$se1/data1$y1)^2
sesq[,4] = (data1$se4/data1$y4)^2 + (data1$se1/data1$y1)^2

V = rep(NA, ns2+ns3+ns4)
V[na>2] = (data1$se1[na>2]/data1$y1[na>2])^2
```

```

dat <- list("nt", "ns2", "ns3", "ns4", "t", "y", "sesq", "V", "na")

#=====
===
# Normal likelihood, identity link, trial-level data given as treatment differences
# Contrast-based random effects consistency model, modified for ratio of means
analysis
#=====
===

trt_diff_norm_consist <- function() { # ***
PROGRAM STARTS
  for (i in 1:ns2) { # LOOP
THROUGH 2-ARM STUDIES
  y[i,2] ~ dnorm(delta[i,2], prec[i,2]) #
Normal likelihood for 2-arm trials
  resdev[i] <- (y[i,2]-delta[i,2])*(y[i,2]-delta[i,2])*prec[i,2] #
Deviance contribution for trial i
  resdev.contrast[i,1] <- resdev[i]
  }

  for (i in (ns2+1):(ns2+ns3)) { # LOOP
THROUGH 3-ARM STUDIES
  for (k in 1:(na[i]-1)) { # set
variance-covariance matrix
  for (j in 1:(na[i]-1)) {
    Sigma[i,j,k] <- V[i]*(1>equals(j,k)) + sesq[i,k+1]*equals(j,k)
  }
  }
  Omega[i,1:(na[i]-1),1:(na[i]-1)] <- inverse(Sigma[i,,]) #
Precision matrix
  y[i,2:na[i]] ~ dnorm(delta[i,2:na[i]], Omega[i,1:(na[i]-1),1:(na[i]-1)]) #
Normal likelihood for 3-arm trials
  for (k in 1:(na[i]-1)) { #
multiply vector & matrix
  ydiff[i,k] <- y[i,(k+1)] - delta[i,(k+1)]
  z[i,k] <- inprod(Omega[i,k,1:(na[i]-1)], ydiff[i,1:(na[i]-1)])
  resdev.contrast[i,k] <- ydiff[i,k] * z[i,k]
  }
  resdev[i] <- inprod(ydiff[i,1:(na[i]-1)], z[i,1:(na[i]-1)]) #
Deviance contribution for trial i
  }

  for (i in (ns2+ns3+1):(ns2+ns3+ns4)) { # LOOP
THROUGH 4-ARM STUDIES
  for (k in 1:(na[i]-1)) { # set
variance-covariance matrix
  for (j in 1:(na[i]-1)) {
    Sigma2[i,j,k] <- V[i]*(1>equals(j,k)) + sesq[i,k+1]*equals(j,k)
  }
  }
  Omega2[i,1:(na[i]-1),1:(na[i]-1)] <- inverse(Sigma2[i,,]) #
Precision matrix
  y[i,2:na[i]] ~ dnorm(delta[i,2:na[i]], Omega2[i,1:(na[i]-1),1:(na[i]-1)]) #
Normal likelihood for 4-arm trials
  for (k in 1:(na[i]-1)) { #
multiply vector & matrix

```

```

ydiff[i,k] <- y[i,(k+1)] - delta[i,(k+1)]
z[i,k] <- inprod(Omega2[i,k,1:(na[i]-1)], ydiff[i,1:(na[i]-1)])

resdev.contrast[i,k] <- ydiff[i,k] * z[i,k]
}
resdev[i] <- inprod(ydiff[i,1:(na[i]-1)], z[i,1:(na[i]-1)]) #
Deviance contribution for trial i
}

for (i in 1:(ns2+ns3+ns4)){ # LOOP THROUGH ALL STUDIES
  w[i,1] <- 0 # adjustment for multi-arm trials
  is 0 for control arm
  delta[i,1] <- 0 # treatment effect is 0 for
  control arm
  for (k in 2:na[i]){ # LOOP THROUGH ARMS
    prec[i,k] <- 1/sesq[i,k] # set precisions
  }

  for (k in 2:na[i]){ # LOOP THROUGH ARMS
    delta[i,k] ~ dnorm(md[i,k], taud[i,k]) # trial-specific treatment
  }
  effects distributions
  md[i,k] <- d[t[i,k]] - d[t[i,1]] + sw[i,k] # mean of trmt effects
  distributions (with multi-arm correction)
  taud[i,k] <- tau *2*(k-1)/k # precision of effects
  distributions (with multi-arm correction)
  w[i,k] <- (delta[i,k] - d[t[i,k]] + d[t[i,1]]) # adjustment for multi-arm RCTs
  sw[i,k] <- sum(w[i,1:k-1])/(k-1) # cumulative adjustment for
  multi-arm trials
}
}
totresdev <- sum(resdev[]) # total residual deviance
d[1] <- 0 # treatment effect is 0 for
reference treatment
for (k in 2:nt){
  d[k] ~ dnorm(0, 0.01) # vague priors for treatment
}
effects
}
sd ~ dunif(0, 3) # vague prior for between-trial
SD
tau <- pow(sd, -2) # between-trial precision =
(1/between-trial variance)

# Output
# pairwise treatment effect for all possible pair-wise comparisons, if nt>2
for (c in 1:(nt-1)) {
  for (k in (c+1):nt) {
    logRoM[c,k] <- d[k] - d[c]
    logRoM[k,c] <- d[c] - d[k]
    RoM[c,k] <- exp(logRoM[c,k])
    better[c,k] <- step(logRoM[c,k]) # assumes a positive result
  }
}
is "good"
}

# ranking on relative scale
for (k in 1:nt) {
  rk[k] <- nt+1-rank(d[,k]) # assumes events are "good"
}

```

```

    best[k] <- equals(rk[k],1) # calculate probability that
  treat k is best
    for (i in 1:nt){
      prk[i,k] <- equals(rk[k],i) # calculate probability of
  treat k being each rank i
    }
  }

  for (k in 1:nt) {
    for (h in 1:nt){
      cumeffectiveness[k,h] <- sum(prk[1:h,k]) # Cumulative ranking prob of
  trmt k to be among the h best
    }
    SUCRA[k] <- sum(cumeffectiveness[k, 1:(nt-1)])/(nt-1) # Surface Under the
  Cumulative RANKings for treatment k
  }
} # *** PROGRAM ENDS

write.model(trt_diff_norm_consist, "trt_diff_norm_consist.txt")
MODELFILE <- c("trt_diff_norm_consist.txt")

# Initial Values
inits <- NULL

parameters <- c("d", "sd", "delta", "logRoM", "RoM",
               "best", "better", "prk", "rk", "SUCRA",
               "resdev.contrast", "resdev", "totresdev")

NMA.sim <- bugs(dat, inits, parameters, model.file = MODELFILE,
               n.chains = 2, n.iter = NITER, n.burnin = NBURNIN,
               DIC = TRUE, debug = FALSE, save.history = FALSE,
               codaPkg = FALSE, working.directory = WD, clearWD = FALSE)

```

Part B. Contrast-based random effects unrelated means model, modified for ratio of means analysis

```

=====
===
# Normal likelihood, identity link, trial-level data given as treatment differences
# Contrast-based random effects unrelated means model, modified for ratio of means
analysis
=====
===

trt_diff_norm_unrelat <- function() { # ***
PROGRAM STARTS
  for (i in 1:ns2){ # LOOP
THROUGH 2-ARM STUDIES
  y[i,2] ~ dnorm(delta[i,2], prec[i,2]) #
Normal likelihood for 2-arm trials
  resdev[i] <- (y[i,2]-delta[i,2])*(y[i,2]-delta[i,2])*prec[i,2] #
Deviance contribution for trial i
  resdev.contrast[i,1] <- resdev[i]
}

```

```

for (i in (ns2+1):(ns2+ns3)){ # LOOP
THROUGH 3-ARM STUDIES
  for (k in 1:(na[i]-1)){ # set
variance-covariance matrix
  for (j in 1:(na[i]-1)){
    Sigma[i,j,k] <- V[i]*(1>equals(j,k)) + sesq[i,k+1]*equals(j,k)
  }
  }
  Omega[i,1:(na[i]-1),1:(na[i]-1)] <- inverse(Sigma[i,,]) #
Precision matrix
  y[i,2:na[i]] ~ dnorm(delta[i,2:na[i]], Omega[i,1:(na[i]-1),1:(na[i]-1)]) #
Normal likelihood for 3-arm trials
  for (k in 1:(na[i]-1)){ #
multiply vector & matrix
  ydiff[i,k] <- y[i,(k+1)] - delta[i,(k+1)]
  z[i,k] <- inprod(Omega[i,k,1:(na[i]-1)], ydiff[i,1:(na[i]-1)])
  resdev.contrast[i,k] <- ydiff[i,k] * z[i,k]
  }
  resdev[i] <- inprod(ydiff[i,1:(na[i]-1)], z[i,1:(na[i]-1)]) #
Deviance contribution for trial i
  }

for (i in (ns2+ns3+1):(ns2+ns3+ns4)){ # LOOP
THROUGH 4-ARM STUDIES
  for (k in 1:(na[i]-1)){ # set
variance-covariance matrix
  for (j in 1:(na[i]-1)){
    Sigma2[i,j,k] <- V[i]*(1>equals(j,k)) + sesq[i,k+1]*equals(j,k)
  }
  }
  Omega2[i,1:(na[i]-1),1:(na[i]-1)] <- inverse(Sigma2[i,,]) #
Precision matrix
  y[i,2:na[i]] ~ dnorm(delta[i,2:na[i]], Omega2[i,1:(na[i]-1),1:(na[i]-1)]) #
Normal likelihood for 4-arm trials
  for (k in 1:(na[i]-1)){ #
multiply vector & matrix
  ydiff[i,k] <- y[i,(k+1)] - delta[i,(k+1)]
  z[i,k] <- inprod(Omega2[i,k,1:(na[i]-1)], ydiff[i,1:(na[i]-1)])
  resdev.contrast[i,k] <- ydiff[i,k] * z[i,k]
  }
  resdev[i] <- inprod(ydiff[i,1:(na[i]-1)], z[i,1:(na[i]-1)]) #
Deviance contribution for trial i
  }

for (i in 1:(ns2+ns3+ns4)){ # LOOP THROUGH ALL STUDIES
  w[i,1] <- 0 # adjustment for multi-arm trials
is 0 for control arm
  delta[i,1] <- 0 # treatment effect is 0 for
control arm
  for (k in 2:na[i]){ # LOOP THROUGH ARMS
    prec[i,k] <- 1/sesq[i,k] # set precisions
  }

  for (k in 2:na[i]){ # LOOP THROUGH ARMS
    delta[i,k] ~ dnorm(md[i,k], taud[i,k]) # trial-specific treat effects
distributions
  }
}

```

```

    md[i,k] <- di[t[i,1],t[i,k]] + sw[i,k]           # mean of trmt effects
distributions (with multi-arm correction)
    taus[i,k] <- tau *2*(k-1)/k                   # precision of effects
distributions (with multi-arm correction)
    w[i,k] <- delta[i,k] - di[t[i,1],t[i,k]]       # adjustment for multi-arm RCTs
    sw[i,k] <- sum(w[i,1:k-1])/(k-1)               # cumulative adjustment for
multi-arm trials
}
}
totresdev <- sum(resdev[])                          # total residual deviance

for (c in 1:(nt-1)) {                               # priors for all mean treatment
effects
  for (k in (c+1):nt) {
    di[c,k] ~ dnorm(0, 0.01)
  }
}

sd ~ dunif(0, 3)                                     # vague prior for between-trial
SD
tau <- pow(sd, -2)                                   # between-trial precision =
(1/between-trial variance)
}                                                     # *** PROGRAM ENDS

write.model(trt_diff_norm_unrelat, "trt_diff_norm_unrelat.txt")
MODELFILE <- c("trt_diff_norm_unrelat.txt")

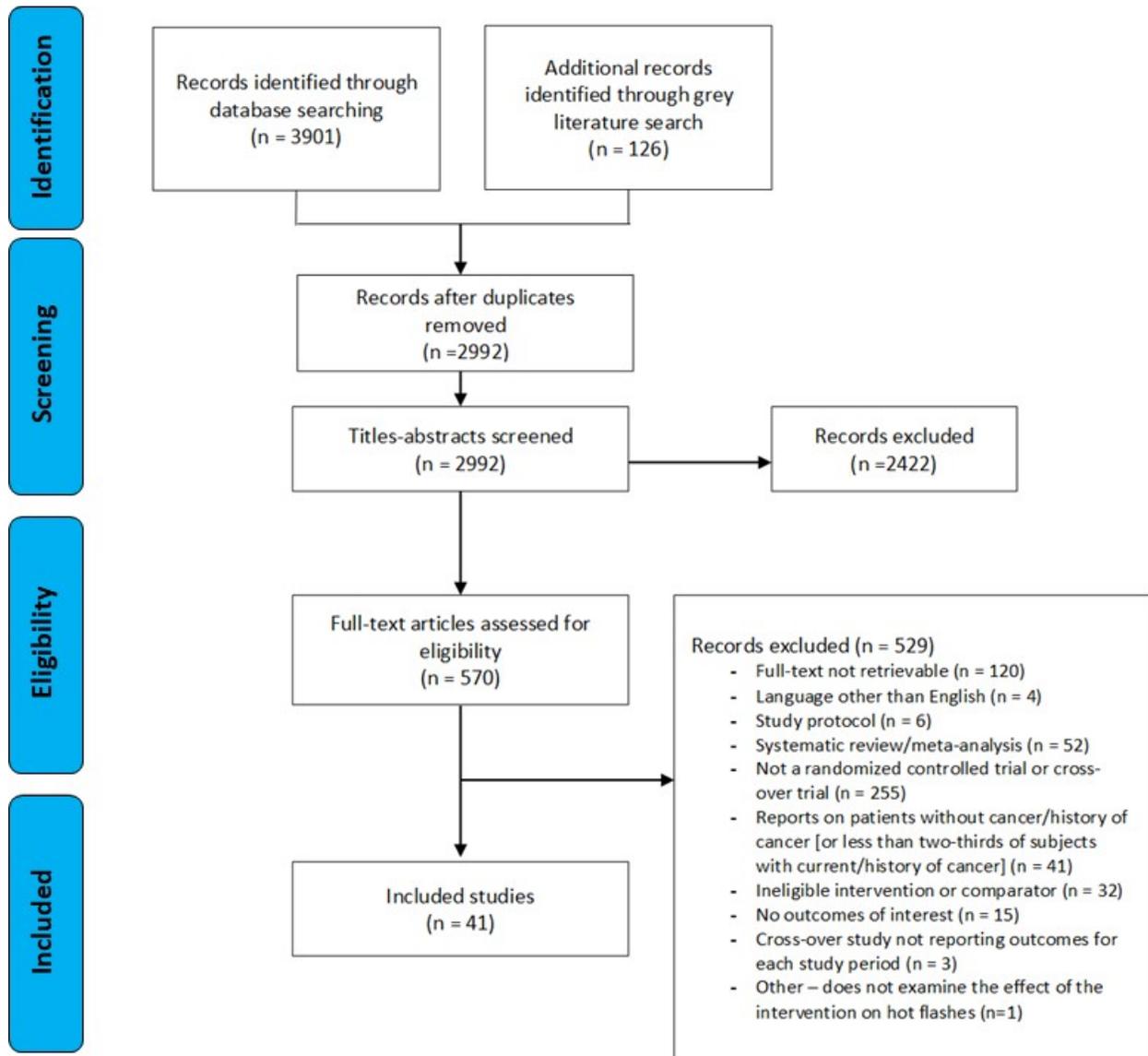
# Initial Values
inits <- NULL

parameters <- c("di", "sd", "delta", "resdev.contrast", "resdev", "totresdev")

NMA.sim <- bugs(dat, inits, parameters, model.file = MODELFILE,
  n.chains = 2, n.iter = NITER, n.burnin = NBURNIN,
  DIC = TRUE, debug = FALSE, save.history = FALSE,
  codaPkg = FALSE, working.directory = WD, clearWD = FALSE)

```

Appendix 4: Flow Diagram of Study Selection Process



Appendix 5: Studies Excluded During Full Text Screening (With Reasons)

Full-text not retrievable (n=120)

Absenger Cancer Education Foundation. A Pilot Study To Assess Guidance in and Subsequent Use of Mind-Body Techniques on the Quality of Life of Cancer Patients.

<http://clinicaltrials.gov/show/NCT01586546> 2012.

Allais, G., Gabellari, I. C., Rolando, S., Borgogno, P., Cormio, M., and Benedetto, C. Use of acupuncture in the treatment of climacteric disorders. *Giornale Italiano di Ostetricia e Ginecologia* 2009. 31 (1-2): 68-69.

Alliance for Clinical Trials in Oncology. Soy Protein Supplement In Treating Hot Flashes in Postmenopausal Women Receiving Tamoxifen for Breast Disease.

<https://clinicaltrials.gov/ct2/show/NCT00031720> 2015.

Arneil, M., Anderson, D., Alexander, K., and McCarthy, A. Investigating the impact of physical activity on cognition-related quality of life in younger women after breast cancer treatment. *Asia-Pacific Journal of Clinical Oncology* 2017. 13 (Supplement 4): 207-208.

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Other – does not examine the effect of the intervention on hot flashes (n=1)

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Appendix 6: Reporting of Outcomes by Study

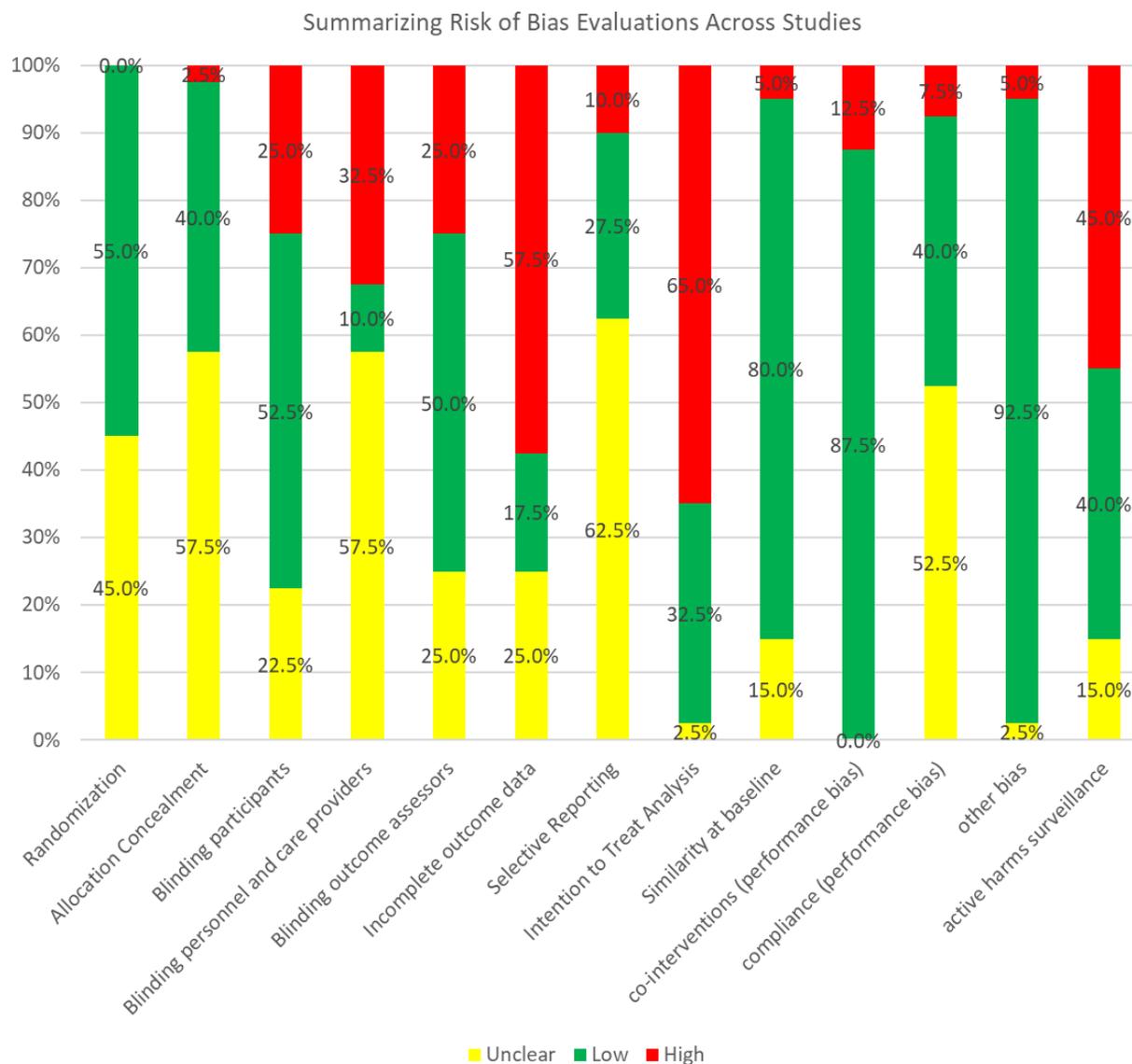
Entries of 'X' are shown to reflect where studies have reported the outcome noted within the header row of each column.

Study	Year	Changes in Patients' Hot Flash Experience			Quality of Life Measures			
		Severity?	Frequency?	Composite (S x F)?	General HR QoL?	Sleep-related?	Depression-related	Sexual function related?
Biglia	2016		X	X			X	
Lesi	2016			X				
Stefanopoulou	2015		X		X		X	
Mao	2015		X	X				
Cramer	2015				X		X	
Chen	2014	X	X	X		X	X	
Bao	2014			X	X	X	X	
Vitolins	2013	X	X	X	X			
Bokmand	2013							
Liljegren	2012		X					
Mann	2012		X			X	X	
Duijts	2012		X		X		X	X
Boekhout	2011			X		X	X	X
Bordeleau	2010	X	X	X	X			
Walker	2010	X	X		X		X	
Loprinzi	2009		X	X	X		X	
Biglia	2009		X	X	X	X		
Wu	2009		X	X	X			
Carson	2009	X	X	X		X		
Frisk	2009		X	X				
Hervik	2009		X					
Elkins	2008		X	X		X	X	
Fenlon	2008	X	X		X			
Loibl	2007	X	X	X				

Study	Year	Changes in Patients' Hot Flash Experience			Quality of Life Measures			
		Severity?	Frequency?	Composite (S x F)?	General HR QoL?	Sleep-related?	Depression-related	Sexual function related?
Deng	2007		X					
Loprinzi	2007		X	X	X			
Kimmick	2006		X	X	X		X	
Nedstrand	2005		X		X			
Stearns	2005		X	X	X	X	X	X
Pandya	2005		X	X				
MacGregor	2005				X			
Hernández Munoz	2003	X						
Van Patten	2002		X	X				
Loprinzi	2002		X	X	X		X	X
Jacobson	2001	X		X	X			
Pandya	2000	X	X	X	X			
Loprinzi	2000		X	X	X		X	X
Quella	2000		X	X				
Fenlon	1999		X					
Barton	1998	X	X	X				

Appendix 7: Findings from Risk of Bias Assessment

An overview of the study risk of bias of the included trials is provided below, followed by a table providing a detailed account of the assessment for each included study. All assessments are based upon the Cochrane Risk of Bias Tool for RCTs (Higgins et al., 2011).



Study	Randomization	Allocation Concealment	Blinding participants	Blinding personnel and care providers	Blinding outcome assessors	Incomplete outcome data	Selective Reporting	Intention to Treat Analysis	Similarity at baseline	co-int (performance bias)	compliance (perf bias)	other bias	active harms surveillance	Overall judgment for efficacy and harms endpoints
Loprinzi (2009)	Green	Green	Green	Green	Red	Yellow	Yellow	Green	Green	Green	Green	Green	Green	Yellow
Bordeleau (2010)	Yellow	Green	Red	Red	Green	Green	Green	Red	Green	Green	Green	Green	Green	Red
Vitolins (2013)	Yellow	Yellow	Green	Yellow	Red	Red	Green	Red	Green	Green	Green	Green	Red	Red
Biglia (2009)	Green	Yellow	Red	Red	Green	Red	Yellow	Red	Green	Green	Yellow	Green	Red	Red
Boekhout (2011)	Yellow	Green	Green	Yellow	Green	Red	Yellow	Red	Green	Green	Yellow	Green	Green	Red
Chen (2014)	Yellow	Green	Green	Yellow	Green	Red	Green	Red	Green	Green	Green	Green	Red	Red
Wu (2009)	Yellow	Yellow	Green	Yellow	Yellow	Yellow	Yellow	Red	Green	Green	Yellow	Green	Green	Red
Carson (2009)	Green	Yellow	Yellow	Green	Green	Green	Yellow	Green	Green	Green	Green	Red	Red	Yellow
Bao (2014)	Green	Red	Green	Green	Red	Red	Green	Red	Green	Green	Yellow	Green	Red	Red
Bokmand (2013)	Yellow	Yellow	Red	Red	Yellow	Green	Green	Green	Green	Red	Yellow	Green	Red	Red
Walker (2010)	Yellow	Yellow	Yellow	Yellow	Green	Red	Yellow	Red	Red	Green	Yellow	Green	Yellow	Red
Frisk (2009)	Yellow	Yellow	Green	Red	Green	Green	Yellow	Red	Yellow	Green	Yellow	Green	Red	Red
Liljegren (2012)	Yellow	Green	Green	Red	Green	Green	Yellow	Red	Green	Green	Green	Green	Red	Red
Loibl (2007)	Green	Green	Green	Yellow	Red	Red	Yellow	Red	Green	Green	Yellow	Green	Green	Red

Study	Randomization	Allocation Concealment	Blinding participants	Blinding personnel and care providers	Blinding outcome assessors	Incomplete outcome data	Selective Reporting	Intention to Treat Analysis	Similarity at baseline	co-int (performance bias)	compliance (perf bias)	other bias	active harms surveillance	Overall judgment for efficacy and harms endpoints
Stefanopoulou (2015)	Green	Yellow	Red	Red	Yellow	Red	Red	Red	Green	Green	Green	Green	Red	Red
Elkins (2008)	Green	Yellow	Yellow	Yellow	Green	Red	Green	Red	Green	Green	Yellow	Green	Red	Red
Deng (2007)	Yellow	Green	Green	Yellow	Yellow	Green	Green	Red	Yellow	Red	Green	Green	Yellow	Red
Fenlon (1999)	Yellow	Green	Yellow	Yellow	Red	Red	Yellow	Red	Yellow	Red	Green	Green	Red	Red
Mao (2015)	Green	Green	Red	Red	Yellow	Red	Green	Green	Green	Green	Green	Green	Green	Red
Fenlon (2008)	Green	Green	Yellow	Yellow	Yellow	Red	Yellow	Red	Green	Red	Red	Green	Red	Red
Mann (2012)	Green	Yellow	Red	Red	Green	Red	Green	Red	Green	Green	Green	Green	Red	Red
Kimmick (2006)	Yellow	Yellow	Green	Yellow	Green	Red	Yellow	Red	Green	Green	Yellow	Green	Green	Red
Hervik (2009)	Yellow	Yellow	Green	Red	Green	Red	Yellow	Red	Green	Green	Yellow	Green	Red	Red
Nedstrand (2005)	Green	Yellow	Green	Yellow	Yellow	Red	Yellow	Red	Green	Green	Yellow	Green	Green	Red
Stearns (2005)	Yellow	Green	Yellow	Yellow	Green	Red	Yellow	Red	Yellow	Green	Red	Green	Red	Red
Pandya (2005)	Green	Yellow	Green	Yellow	Green	Red	Yellow	Red	Green	Green	Yellow	Green	Green	Red
MacGregor (2005)	Green	Yellow	Green	Yellow	Green	Red	Yellow	Red	Red	Red	Yellow	Red	Yellow	Red
Jacobson (2001)	Green	Yellow	Green	Yellow	Yellow	Red	Yellow	Green	Green	Green	Green	Green	Red	Red

Study	Randomization	Allocation Concealment	Blinding participants	Blinding personnel and care providers	Blinding outcome assessors	Incomplete outcome data	Selective Reporting	Intention to Treat Analysis	Similarity at baseline	co-int (performance bias)	compliance (perf bias)	other bias	active harms surveillance	Overall judgment for efficacy and harms endpoints
Barton (1998)	Yellow	Yellow	Yellow	Yellow	Green	Yellow	Yellow	Red	Green	Green	Yellow	Green	Green	Yellow
Van Patten (2002)	Yellow	Yellow	Green	Yellow	Green	Red	Yellow	Red	Green	Green	Green	Green	Yellow	Red
Pandya (2000)	Green	Green	Green	Yellow	Green	Red	Red	Green	Green	Green	Yellow	Green	Green	Red
Loprinzi C (2000)	Green	Green	Green	Green	Red	Yellow	Yellow	Green	Yellow	Green	Yellow	Green	Green	Yellow
Loprinzi C (2007)	Green	Green	Red	Red	Green	Yellow	Yellow	Green	Green	Green	Yellow	Green	Green	Red
Quella (2000)	Green	Yellow	Green	Yellow	Green	Yellow	Yellow	Green	Green	Green	Green	Green	Green	Yellow
Loprinzi C (2002)	Green	Yellow	Green	Green	Red	Yellow	Yellow	Green	Green	Green	Yellow	Green	Green	Yellow
Hernandez Munoz (2003)	Yellow	Yellow	Red	Red	Yellow	Yellow	Yellow	Red	Yellow	Green	Yellow	Green	Yellow	Red
Duijts (2012)	Green	Yellow	Yellow	Yellow	Red	Yellow	Red	Green	Green	Green	Red	Green	Red	Red
Cramer (2015)	Green	Green	Red	Red	Yellow	Green	Green	Green	Green	Green	Green	Green	Red	Red
Biglia (2016)	Yellow	Yellow	Yellow	Yellow	Red	Yellow	Green	Yellow	Green	Green	Green	Yellow	Green	Red
Lesi (2016)	Green	Green	Red	Red	Red	Red	Red	Green	Green	Green	Yellow	Green	Yellow	Red

Appendix 8: Model Fit Statistics from Network Meta-Analyses

Model fit statistics for network meta-analyses related to reductions in hot flash score and hot flash frequency are presented below. As contrast-based models were used to allow for the incorporation of both the absolute measures and the percentages in the estimation of ratios of means, the number of unconstrained data points is equal to the total number of study arms minus the number of comparator arms.

Model	# unconstrained data points	Total residual deviance	Between-study SD (95% CrI)	DIC
Reduction in hot flash score (12 studies)				
RE consistency	20 intervention arms in contrast with 12 comparator arms	20.30	0.20 (0.01 to 0.49)	22.40
RE unrelated means		20.19	0.19 (0.01 to 0.50)	22.58
Reduction in hot flash frequency (11 studies)				
RE consistency	17 intervention arms in contrast with 11 comparator arms	17.76	0.29 (0.04 to 0.66)	20.78
RE unrelated means		17.52	0.34 (0.07 to 0.77)	21.33

Appendix 9: Checking the Consistency Assumption for NMAs

After fitting the RE consistency model and unrelated means model with the same treatment coding assigned to different doses of a regimen, we plotted the posterior mean residual deviance of every contrast (instead of plotting the posterior mean deviance contributions of every arm from an arm-based model) and of every study. In addition to review of model fit statistics (DIC) to assess support for the consistency assumption, plots of deviance residuals were also assessed. These are provided below.

Hot flash score: Loprinzi et al 2000 had three contrasts of different doses of venlafaxine against placebo: venlafaxine 37.5mg/d vs. placebo had smaller residual deviance from the RE consistency model than from the RE unrelated means model, while venlafaxine 75mg/d vs. placebo and venlafaxine 150mg/d vs. placebo had larger residual deviance from the RE consistency model than from the RE unrelated means model (Figure A1). When we plotted posterior mean residual deviance of every study, however, the residual deviance measures of Loprinzi et al 2000 from both models were close. This may relate to the diverse effect sizes reported for different doses of venlafaxine in Loprinzi et al 2000, but not for venlafaxine as a whole. We exercised caution and preferred not to exclude this study.

Hot flash score: As displayed in Figure A2, no severe violation of the consistency assumption had been detected.

Figure A1: posterior mean residual deviance for hot flash score

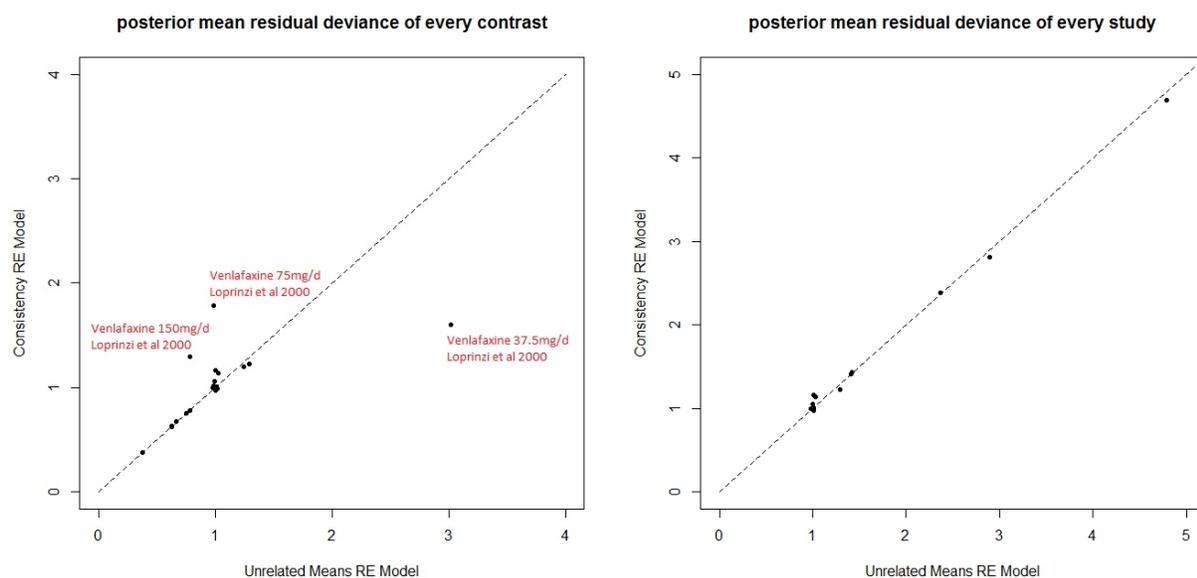
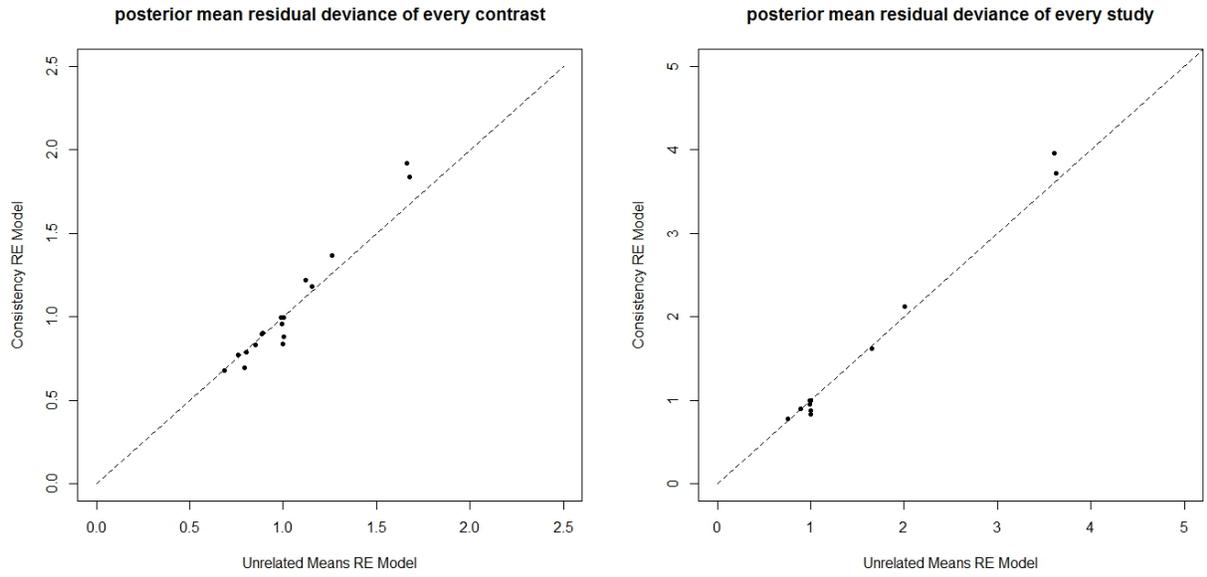


Figure A2: posterior mean residual deviance for hot flash frequency



Appendix 10: Secondary Effect Measures from Network Meta-Analyses

For reductions in hot flash frequency and composite hot flash score, where NMAs were performed, findings from pairwise comparisons were summarized in this review in terms of ratios of means with 95% credible intervals. As is common in applications of NMA, secondary measures of effect were also estimated. The tables below provide numeric details from the random effects model analyses with regard to Surface Under the Cumulative Ranking curve (SUCRA), the probability of each treatment being ranked the best, as well as the mean treatment ranking. For all three parameters, values nearest 1 are indicative of more preferable interventions.

Hot Flash Frequency

Intervention	RE model		
	Mean SUCRA	Mean Pr(best)	Mean Rank
Paroxetine	0.873	0.515	2.02 (1 to 6)
Venlafaxine	0.801	0.188	2.59 (1 to 6)
Gabapentin + AD	0.592	0.086	4.27 (1 to 8)
Sertraline	0.548	0.062	4.61 (1 to 8)
Gabapentin	0.525	0.007	4.80 (2 to 7)
Clonidine	0.518	0.011	4.86 (2 to 8)
Melatonin	0.387	0.13	5.90 (1 to 9)
Placebo	0.224	0	7.21 (5 to 8)
Vitamin E	0.033	0	8.74 (7 to 9)

Composite Hot Flash Score

Intervention	RE model		
	Mean SUCRA	Mean Pr(best)	Mean Rank
Paroxetine	0.872	0.484	2.28 (1 to 7)
Clonidine	0.760	0.110	3.40 (1 to 8)
Electro Acupuncture	0.733	0.138	3.67 (1 to 8)
Venlafaxine	0.589	0.013	5.11 (2 to 9)
Sham Acupuncture	0.569	0.031	5.31 (1 to 9)
Sertraline	0.539	0.052	5.61 (1 to 10)
Gabapentin	0.451	0.001	6.49 (3 to 9)
Gabapentin + AD	0.424	0.021	6.76 (2 to 10)
Melatonin	0.336	0.150	7.64 (1 to 11)
Placebo	0.212	0	8.88 (7 to 10)
Vitamin E	0.016	0	10.84 (10 to 11)

Appendix 11: Summary of Findings, Narrative Summary of A Priori Outcomes and Tolerability

For studies that could not be included in meta-analyses or network meta-analyses, a detailed account of their findings was compiled. These summaries are provided below, with one summary table per outcome for each of the following endpoints: hot flash frequency, hot flash severity, hot flash score, generic quality of life, sleep related quality of life, depression related quality of life, sexual dysfunction related quality of life, and harms. These details have been provided in this supplement to maximize completeness and transparency of this systematic review while maintaining readability of the main text. Green cell coloring has been used to denote studies where effective interventions and/or significant differences between treatments were found, while red cell coloring has been used to denote studies where no such difference was identified.

Hot Flash Frequency: Study Findings		
Study First Author and Year	Treatment Comparison	Findings
Comparisons Involving Pharmacologics		
Biglia 2016	Escitalopram (n=30) vs duloxetine (n=28)	In this study, HFF and HFS were self-reported at baseline and following 4 and 12 weeks of treatment. At 12 weeks, the total number of HF's per week decreased 49.8% in the duloxetine group (p=0.003) and in the escitalopram group they decreased 53% (P=0.001). The conclusion stated by the authors was that both escitalopram and duloxetine had similar efficacy for the relief of HF's in survivors of breast cancer.
Mao 2015	Gabapentin (n=28) vs electroacupuncture (n=30) vs sham acupuncture (n=32) vs placebo (n=30)	The study was for 8 weeks with additional evaluation at week 24 for durability of treatment effects. The mean (SD) daily frequency at baseline for electroacupuncture was 8.3 (5.6), and 6.3 (2.8) for the related sham group; the mean (SD) for the placebo gabapentin arm was 8.1 (5.4), while the related value for the gabapentin group was 6.8 (3.3). The authors concluded that acupuncture produced larger placebo and smaller nocebo effects than did pills for the treatment of hot flashes, however detailed data with regard to frequency were not reported. It was noted that electroacupuncture may be more effective than gabapentin with fewer adverse effects for HF management.
Vitolins 2013	Placebo pill + milk protein powder (n=30) Venlafaxine + milk protein powder (n=30) vs placebo pill + soy (n=30) vs	This study was for 12 weeks. Hot flashes were less frequent in the venlafaxine group in the initial 2 weeks of the study, but this early difference was not sustained at 12 weeks. No difference was noted between the soy and placebo groups throughout the study. The conclusion stated in by the authors was that neither soy nor venlafaxine effectively treated hot flashes over the 12-week study period. They noted the need for additional research for treatment of hot flashes in men with prostate cancer.

Hot Flash Frequency: Study Findings		
Study First Author and Year	Treatment Comparison	Findings
	venlafaxine + soy (n=30)	
Bordeleau 2010	Gabapentin vs venlafaxine; n=66 overall; crossover study	This was a cross-over trial with 2-4 weeks in between study periods. The authors reported that with regard to hot flash frequency, the ratio of venlafaxine compared to gabapentin was 0.94 (95% CI not reported, but the p-value was reported to be >0.61). The authors also reported that 38 of 56 patients completing the study preferred venlafaxine over gabapentin; amongst them, 84.2% felt the frequency of hot flashes was reduced with venlafaxine. The authors concluded that breast cancer survivors prefer venlafaxine over gabapentin for treating hot flashes.
Loprinzi 2002	Fluoxetine vs placebo; n=81 overall; crossover study	The first study period was 5 weeks followed by a second (cross-over) 4-week period. Findings include a decrease in hot flash frequency for patients in the fluoxetine group (3.4 HF per day, 42% decrease) and in the placebo group (2.5 HF per day, 31% decrease) (P=0.54). The conclusion stated by the authors was that the dose of fluoxetine studied resulted in a modest improvement in hot flashes. The authors concluded that this dose of fluoxetine resulted in a modest improvement in hot flashes.
Comparisons Involving Non-Pharmacologics		
Stefanopoulou 2015	CBT (n=33) vs usual care (n=35) (prostate cancer study)	The CBT intervention included a booklet, CD plus telephone contact during a 4-week period. Validated self-report questionnaires were completed at baseline, 6 weeks and 32 weeks after randomisation. There was a significant difference between groups in incidence of weekly HFNS (hot flashes with night sweats) at 6 weeks, with greater reductions from baseline observed in the CBT group compared to the usual care group (adjusted mean difference -12.12, 95% CI -22.39 to -1.84; p =0.02); the corresponding value at 32 weeks was -12.43 (95% CI -28.38 to +3.52). For HF (without night sweats), the adjusted mean differences did not reach statistical significance at either 6 (-4.97, 95% CI -13.09 to 3.14) or 32 weeks (-12.80, 95% CI -25.21 to -3.86). The authors concluded that guided self-help CBT appears to be a safe and effective brief treatment for men who have problematic HFNS following prostate cancer treatments.
Duijts 2012	CBT+exercise (n=106) vs CBT	Self-report questionnaires were completed by patients at baseline, 12 weeks, and 6 months. Findings from intention to treat analyses based on overall model effects

Hot Flash Frequency: Study Findings		
Study First Author and Year	Treatment Comparison	Findings
	(n=109) vs exercise (n=104) vs waitlist (n=103)	indicated statistically significant differences between groups in improvement over time for endocrine symptoms and perceived burden of HFs and night sweats, but not for frequency ratings of HFNS (hot flashes with night sweats).
Liljegren 2012	Acupuncture (n=42) vs sham acupuncture (n=42)	Patients received treatment twice weekly for a duration of 5 weeks. The reductions in frequencies of HFs reached statistical significance at week 6 in both the acupuncture (from baseline mean (SD) 8.4 (5.5) to 5.7 (4.1) at 6 weeks) and sham acupuncture (from baseline 7.1 (4.4) to 4.5 (3.7) at 6 weeks) groups; however, the difference between groups was not statistically significant (mean difference 1.2, 95% CI -0.7 to 3.0; p=0.21).
Mann 2012	CBT (n=47) vs usual care (n=49)	The CBT intervention included a 90-minute group CBT session every week for 6 weeks. Assessments were done at baseline, 9 weeks, and 26 weeks after randomisation. HFNS (hot flashes with night sweats) frequency was measured with the HFNS frequency subscale (total number of HFNS reported in the past week) of the Hot Flush Rating Scale. No statistically significant differences in HFNS frequency, HF frequency and NS frequency subscales were identified at 9 weeks or 26 weeks. Compared with baseline, both groups reported non-significantly fewer HFNS at 9 weeks (21% reduction in the CBT group and 24% reduction in the usual care group) and 26 weeks (38% reduction in both groups). There was little change in 24hr rate of HFNS at 9 weeks. The authors concluded that CBT and usual care resulted in a 38% reduction in HFNS frequency compared with baseline values.
Carson 2009	Yoga (n=17) vs waitlist (n=20)	Study participants were enrolled in an 8-week yoga program or to wait-list control. Daily reports of hot flashes at baseline, post treatment, and 3 months after treatment were captured via an interactive telephone system. Patients' average daily frequency of hot flashes at baseline were 4.40 in the yoga group (range 1.56 to 8.64) and 4.27 (range 1.21 to 8.71) in the control group. Analyses conducted both after completion of treatment (Yoga from daily mean HF frequency 4.44 to 3.73 versus waitlist from 4.29 to 4.40) as well as 3 months later (Yoga from daily mean HF frequency 4.46 to 3.19 versus waitlist from 4.34 to 4.42) identified statistically significant reductions in HF frequency with yoga compared to control.

Hot Flash Frequency: Study Findings		
Study First Author and Year	Treatment Comparison	Findings
Frisk 2009	Acupuncture (n=16) vs electroacupuncture (n=15)	There was no significant difference between the acupuncture and electroacupuncture groups over time ($p=0.25$; ANOVA), however, hot flushes did decrease significantly in both groups and remained decreased at all time points, except for 12 months. The differences in hot flushes per 24 hours decreased from a median of 7.6 at baseline to 4.1 at 12 weeks in the electroacupuncture group and from a median of 5.7 to 3.4 at 12 weeks in the acupuncture group ($p=0.001$). The authors concluded that both electroacupuncture and acupuncture lowered number of HFs.
Hervik 2009	Acupuncture (n=30) vs sham acupuncture (n=29)	Patients were provided with twice weekly acupuncture or sham acupuncture for the first 5 weeks, and subsequently once per week for the next 5 weeks. Daytime HFs were significantly reduced in the acupuncture group (from baseline mean (SD) 9.5 (4.9) to 4.7 (3.7) at 10 weeks, which further reduced to 3.2 (2.2) over the next 12 weeks), while no significant change was seen within the sham acupuncture group (from baseline mean (SD) 12.3 (7.3) to 11.7 (8.5) at 10 weeks, which increased back to 12.1 (8.3) over the next 12 weeks). Similar patterns were reported for nighttime HFs. The difference in acupuncture versus sham acupuncture was statistically significant for both daytime and nighttime HFs.
Elkins 2008	Hypnosis (n=30) vs waitlist (n=30)	There were 5 weeks of sessions, with follow-up focused on HF frequency at baseline and post-test. ANCOVAs (using pre-test HF frequency as a covariate) identified a statistically significant improvement for the hypnosis group compared with the control group (detailed data not reported). The authors concluded that hypnosis appears to reduce perceived hot flashes in breast cancer survivors and may have additional benefits such as reduced anxiety and depression, and improved sleep.
Fenlon 2008	Relaxation (n=74) vs no treatment (n=76)	At baseline, there were median (IQR) numbers of flashes per week of 31.5 (20-45) in the relaxation group and 37 (IQR 20-81) in the control group. After the one-month study period, there was a median improvement of seven flashes per week compared to an improvement of 1 in the control group (median difference in improvement 7, 95% CI 4 to 11; $p<0.001$). After three months, the corresponding improvements were 11 and 4, respectively (median difference in improvement 5, 95% CI 0-10; $p=0.06$). The authors concluded the study showed a small but significant reduction in the incidence of HF with relaxation.

Hot Flash Frequency: Study Findings		
Study First Author and Year	Treatment Comparison	Findings
Deng 2007	Acupuncture (n=42) vs sham acupuncture (n=30)	The protocol included twice weekly treatments for 4 weeks with evaluations at baseline, 6 weeks and 6 months. Patients in the sham group were crossed over to acupuncture at week 7. At week 6 no difference was noted between groups (95% CI, -0.7 to 2.4; p=0.3). At week 12 HFF reduced from 7.3 to 5.4 and treatment improvements were sustained at 6 months. Although HFF was reduced following acupuncture the reduction was not statistically significant.
Nedstrand 2005	Relaxation (n=19) vs electroacupuncture (n=19)	This was a 12-week study comparing relaxation therapy with electroacupuncture. The number of daily HFs was registered in a logbook before and during treatment and after 3 and 6 months of follow-up. For the outcome of HFF, after an initial, statistically significant improvement was seen at 4 weeks, no long-term decreases were seen at 6 months. The conclusion of the authors was that additional research is needed on relaxation and electroacupuncture for treatment of hot flashes.
Van Patten 2002	Soy (n=59) vs placebo (n=64)	This study included a 4-week lead-in phase and 12-week treatment phase involving assignment to a soy or placebo beverage. There were no statistically significant differences between the soy and placebo groups in the mean reductions of daytime (-1.2 soy vs -1.8 placebo), night time (-0.5 soy vs -0.7 placebo) or 24-hr (-1.8 soy vs -2.5 placebo) HFs; however, presumably because of a strong placebo effect, both groups had significant reductions in hot flashes. The authors concluded that the soy beverage did not alleviate HFs any more than placebo.
Quella 2000	Soy (n=88) vs Placebo (n=88) (crossover trial)	This study compared soy tablets to placebo. Following a 1-week lead-in patients received 4 weeks of soy followed by 4 weeks of placebo or the opposite schedule. The study was double blinded and patients self-reported HFF, hot flash intensity and side effects. Among patients receiving placebo, 36% reported that HF frequency was halved, compared with only 24% of patients receiving soy (P =0.01). The authors concluded that the soy product did not alleviate HFs in breast cancer survivors.
Fenlon 1999	Relaxation (n=8) vs no trt (n=8)	The study was for one month and the median was 1-year post treatment with a range of 3 months to 5 years. When comparing the change in hot flushes between the two groups, there appeared to be a trend to reduce both the frequency of hot flushes and associated distress, but none of these differences were shown to be significant. There was an apparent increase in the amount of hot flushes and distress factor in the control

Hot Flash Frequency: Study Findings		
Study First Author and Year	Treatment Comparison	Findings
		group. This was not statistically significant. The authors concluded that a trend was seen for HFs and night sweats to be reduced, but the results did not achieve significance.
Barton 1998	Vitamin E (n=54) vs placebo (n=50) (crossover trial)	This study compared vitamin E 800 IU to placebo. Following a 1-week lead-in, patients received 4 weeks of vitamin E followed by 4 weeks of placebo or the opposite schedule. At the first check at 4 weeks, no difference was found between interventions (decrease of 25% with vitamin E compared with 22% decrease with placebo, p=.90). Incorporating the second study period, a small but statistically significant advantage favouring Vitamin E was noted (suggesting approximately 1 less HF per day). The authors noted that while a significant reduction in HF frequency was seen with vitamin E, clinical relevance was small.

Hot Flash Score: Study Findings		
Study First Author and Year	Treatment Comparison	Findings
Comparisons Involving Pharmacologics		
Biglia 2016	Escitalopram (n=30) vs duloxetine (n=28)	HF score was assessed at both 4 and 12 weeks of treatment. At the end of the study period, the decrease in weekly HF score was 53.6% in the duloxetine group (P=0.003) and 60.4% in the escitalopram group (P=0.001). While both groups demonstrated a significant reduction from baseline, the difference between interventions was not statistically significant. The authors concluded that their data showed that a 12-week treatment both with escitalopram and duloxetine is effective for HF management.
Boekhout 2011	Venlafaxine (n=41) vs clonidine (n=41) vs placebo (n=20)	Daily HF score was calculated as the sum of HF severity values experienced in a given day. At 12 weeks, venlafaxine and clonidine were both associated with lower median HF scores compared to placebo; the median (IQR) scores for the 3 groups were as follows: Placebo - median 10.9, IQR 7.4-15.8; Clonidine: median 7.5, IQR 2.0-10.8; Venlafaxine: median 7.6, IQR 4.0-110.4. It was also noted that when considering the entire 12-week study period, HF score reduction was greater overall with venlafaxine than clonidine due to an earlier start of benefits during the 12-week

Hot Flash Score: Study Findings		
Study First Author and Year	Treatment Comparison	Findings
		period. The study authors concluded that venlafaxine and clonidine are effective treatments in the management of HFs.
Bordeleau 2010	Gabapentin vs venlafaxine (n=66 overall; crossover trial)	Daily HF score was assessed as average HF severity that day x frequency of HFs that day. Treatment periods lasted 4 weeks, with 2-4 weeks washout in between. Findings performed to compare the intervention groups using a mixed modeling approach identified a venlafaxine to gabapentin ratio of 0.96 (near 1), suggesting little difference between intervention groups (p value >0.61); both groups were noted to have important reductions from baseline (from week 2 mean (SD) 18.7 (23.2) to 5.7 (4.6) for venlafaxine in the first study period; from 18.6 (15.4) to 6.5 (8.3) in the gabapentin group). Analyses were also performed to compare groups as based upon patients' preferred treatment; those that preferred venlafaxine (n=38) were reported to experience scores 41% lower, while those that preferred gabapentin (n=18) were reported to experience scores 47% lower.
Frisk 2009	Acupuncture (n=13) vs electroacupuncture (n=11) (prostate cancer trial)	Daily HF distress calculated by summing individual HF distress (scored from 0-10). After 52 weeks of treatment, mean daily HF distress changed from baseline median 7.6 (IQR 4.7-8.3) to median 4.3 (IQR 1.3 – 7.7 in the acupuncture group and from baseline median 8.2 (IQR 6.5-10.7) to median 5.5 (IQR 3.8-6.9) in the electroacupuncture group (p=0.65 between groups).
Loprinzi 2002	Fluoxetine vs placebo (n=81 total; crossover trial)	In the first study period, HF scores decreased by a median of 4.7 units per day (36%) for those on placebo and by 6.4 units per day (50%) in those receiving fluoxetine, and the difference was not statistically significant between groups (P = 0.35). Subsequent cross-over analyses identified a significantly greater reduction with fluoxetine. The authors concluded that fluoxetine was associated with a modest improvement in HF score.
Comparisons Involving Non-Pharmacologies		
Lesi 2016	Acupuncture + enhanced self-care (n=85) vs enhanced self-care (n=105)	The HF score was calculated by multiplying the mean number of daily hot flashes that occurred during the week before assessment by the mean daily severity (1, mild; 2, moderate; 3, severe). After having comparable mean HF scores at baseline, the HF score at week 12 was higher in the enhanced self group (mean (SD) 22.70 (19.40)) than in the acupuncture + enhanced self-care group (11.34 (14.75); p<0.001 for the

Hot Flash Score: Study Findings		
Study First Author and Year	Treatment Comparison	Findings
		between-group difference of -11.36, 95% CI -16.39 to -6.33). Similar mean differences favoring the acupuncture + enhanced self-care group were seen at both 3-month (-7.86, 95% CI -12.99 to -2.73) and 6-month follow-up (-8.82, 95% CI -14.04 to -3.61). The authors concluded that acupuncture in association with enhanced self-care is an effective integrative intervention for managing HFs.
Bao 2014	Acupuncture (n=25) vs sham acupuncture (n=26)	HF score was determined using a 100-point visual analog scale (VAS) ≥ 20 . The study presents comparison of median (IQR) scores between groups after 8 weeks of treatment. The change in the sham acupuncture group wasn't statistically significant (from median (IQR) 20.5 (54.75) to 10 (47.25)), while the change in the acupuncture group was significant (from median (IQR) 31 (67) to 14 (32.5)); the comparison of change between groups was not statistically significant (p=0.56). The authors reported no important differences between interventions.
Vitolins 2013	Venlafaxine+soy protein (n=30) vs venlafaxine+milk protein (n=30) vs soy protein (n=30) vs milk protein (n=30) (prostate cancer trial)	The study reported that there were no statistically significant differences between the soy and placebo arms at any time, and although participants in the venlafaxine arm tended to have fewer hot flashes during the initial 2 weeks, this early difference had disappeared by 12 weeks; mean (SD) 12-week HF score values were as follows: venlafaxine + soy protein – 11.2 (10.9); venlafaxine + milk protein – 9.2 (7.2); placebo + soy protein – 13.6 (15.3); placebo + milk protein – 9.3 (8.5). The authors concluded that in androgen-deprived men, neither venlafaxine nor soy proved effective in reducing HFs.
Carson 2009	Yoga (n=17) vs waitlist control (n=17)	Statistically significant improvements in the yoga group both post-treatment (yoga group: from mean score change 20.92 to 14.46 vs control group: mean score change from 23.01 to 25.81) and at 3-month follow-up. This pilot study provides promising support for the beneficial effects of a comprehensive yoga program for management of HFs and other menopausal symptoms.
Elkins 2008	Hypnosis (n=30) vs waitlist control (n=30)	The authors used the Hot Flash Related Daily Interference Scale, based upon HF frequency and severity. Patients in the hypnosis group demonstrated statistically significantly better improvement in HF score (from baseline mean (SD) 15.05 (13.75) to 4.84 (5.02)) compared to those in the control group (from baseline mean (SD) 17.17

Hot Flash Score: Study Findings		
Study First Author and Year	Treatment Comparison	Findings
		(10.37) to 15.60 (10.71); p<.001). The authors concluded that hypnosis appears to reduce HFs in breast cancer survivors.
Van Patten 2002	Soy (n=78) vs placebo (n=79)	HF score was assessed according to: [hot flash frequency x severity for day] + [hot flash frequency x severity for night] for 24 hours. The study reported there were no differences in hot flash related outcomes between groups: during the final 4 weeks of treatment, comparable changes from baseline in the soy group (mean (SD) change from baseline 18.0 (13.9) to final value 12.6 (13.4)) and placebo groups (mean (SD) change from baseline 18.9 (18.9) to final value 11.4 (11.3)) were observed.
Jacobson 2001	Black cohosh (n=42) vs placebo (n=43)	The HF score used was unclear in the study report. After 9 weeks, the HF score changed from baseline median 53.2 (IQR 25.3-71.3) to 31.0 (IQR 18.3-77.0) in the black cohosh group and from median 52.5 (IQR 28.9-93.0) to median 24.6 (IQR 16.4-64) in the placebo group; the difference was noted as not statistically significant, but no other data were provided.
Quella 2000	Soy (n=87) vs placebo (n=88)	Patients averaged approximately seven HFs per day during the baseline study week (SD 54.5), with an average HF score of 13 points (SD 59.0). The totals of patients reporting reductions in HF score of <25%, 25-50% and >50% were 44%, 21% and 35% in the soy group and 40%, 22% and 38% in the placebo group, respectively. The authors concluded that the available data strongly suggest that soy phytoestrogens do not substantially reduce HFs when compared with placebo
Barton 1998	Vitamin E vs placebo (n=104 total; crossover trial)	HF score was calculated as the product of frequency x severity. After the first 4 weeks of therapy, the HF score decreased by 28% with vitamin E and 20% with placebo (P = 0.68). During the second treatment period, the mean hot-flash scores decreased by 0.03% and 25% in the placebo group and vitamin E group (P=0.24), respectively. A subsequent analysis encompassing the full crossover design suggested the presence of a small but statistically significant advantage of vitamin E over placebo.

Hot Flash Severity: Study Findings		
Study First Author and Year	Treatment Comparison	Findings
Comparisons Involving Pharmacologics		

Hot Flash Severity: Study Findings		
Study First Author and Year	Treatment Comparison	Findings
Bordeleau 2010	Gabapentin vs venlafaxine (n=66 overall; crossover trial)	HF severity was assessed as 1=mild, 2=moderate, 3=severe, 4=severe, and were averaged per day. Study treatment periods lasted 4 weeks, with 2-4 weeks washout in between. Findings performed to compare the intervention groups using a mixed modeling approach identified a venlafaxine to gabapentin ratio of 1.02 (near 1), suggesting little difference between intervention groups (p value >0.61). Analyses were also performed to compare groups as based upon patients' preferred treatment; amongst those that preferred venlafaxine (n=38), 94.7% reported decreased HF severity, while amongst those that preferred gabapentin (n=18), 94.4% reported decreased HF severity.
Walker 2010	Venlafaxine (n=25) vs acupuncture (n=25)	Treatments were provided for 12 weeks, with outcomes measured up to 1 year post-treatment. The study reported that ANOVA analysis of patient data over time found no important differences between intervention groups with regard to changes in HF severity (p>0.05; detailed numeric data are not reported). Both groups experienced some improvement, with a subsequent return toward baseline values after the end of treatment. The authors suggested acupuncture may offer similar benefits as venlafaxine, with better tolerability.
Loibl 2007	Clonidine (n=40) vs venlafaxine (n=40)	The duration of this study was 4 weeks of treatment. HF severity was scored as 1=mild, 2=moderate, 3=severe, 4=very severe. The mean HF severity at baseline week was 2.1 for clonidine and 1.9 for venlafaxine with a P-value of 0.78. Findings for this outcome are not clearly reported in the study report. Author conclusions appear to suggest benefits of venlafaxine over clonidine for reduction of HF frequency, but not HF severity.
Pandya 2000	Clonidine (n=99) vs placebo (n=99)	The study included a 1-week baseline period and follow-up at 4, 8 and 12 weeks; HFs were scored as 1=mild, 2=moderate, 3=severe, 4=very severe). Mean (SE) severity grades at baseline were 2.2 (0.1) and 2.1 (0.1) in the clonidine and placebo groups, respectively. The study reported % changes from these baseline values; median reductions of -11.7%, -17.3% and -9.3% were reported at 4, 8 and 12 weeks in the clonidine group while corresponding values of -8.5%, -10.5% and -8.3% were observed with placebo. None of the differences reached statistical significance.
Non-Pharmacologic Interventions		

Hot Flash Severity: Study Findings		
Study First Author and Year	Treatment Comparison	Findings
Chen 2014	Melatonin (n=48) vs placebo (n=47)	The study duration was 4 months, and HF severity was scored as 1=mild, 2=moderate, 3=severe, 4=very severe. The study denotes that there were no statistically significant differences between the groups with regard to changes in the numbers of mild, moderate and severe HFs experienced.
Vitolins 2013	Placebo pill + milk protein powder (n=30) Venlafaxine + milk protein powder (n=30) vs placebo pill + soy (n=30) vs venlafaxine + soy (n=30) (prostate cancer study)	The duration reported findings at 4, 8 and 12 weeks; HF severity was scored as 1=mild, 2=moderate and 3=severe. There were no significant differences in the comparison of soy and placebo at any time point. The venlafaxine arm tended to have lower HF severity values at weeks 1, 2, 3, and 4, though the difference was not significant at 12 weeks.
Carson 2009	Yoga (n=17) vs waitlist control (n=20)	The study lasted 8 weeks and included a 3-month follow-up; HF severity was scored on a scale from 0-9 (higher scores denoting higher severity). Findings identified significant improvements with yoga compared to the control group in daily HF severity (as well as frequency and score); in the yoga group, mean score improved from 4.16 to 3.21 post-treatment, while mean score in the control group shifted from 4.67 to 4.41 ($p < 0.01$ for the difference between groups). Similar values were also observed 3 months after treatment. The authors suggested the study provides promising support for the beneficial effects of a comprehensive yoga program for HFs and other menopausal symptoms.
Fenlon 2008	Relaxation (n=74) vs no trt (n=76)	The study occurred over one month. The severity of HFs, as recorded by diaries, significantly declined over one month in the relaxation group compared with the control group ($P < 0.01$). The authors concluded the study showed a small, but statistically significant reduction in the incidence and severity of HFs associated with relaxation therapy.
Hernandez Munoz 2003	Black cohosh (90) vs usual care (46)	Patients were compared in terms of the % free of hot flashes, % still having moderate hot flashes (a few episodes of heat with discrete sweating), and % still having severe hot flashes (>5 or more sudden episodes of heat are experienced during the day,

Hot Flash Severity: Study Findings		
Study First Author and Year	Treatment Comparison	Findings
		accompanied by sweating, sleep disturbances, feeling of irritation and anxiety) at study end. At the 52-week conclusion of the study, the proportions of patients who were free of hot flashes/still endured moderate hot flashes/still endured severe hot flashes were different between those receiving black cohosh (46.7%, 28.9%, and 24.4%) compared to usual care (0%, 26.1%, and 73.9%).
Jacobson 2001	Black cohosh (n=42) vs placebo (n=43)	Patients completed HF diaries at 30 and 60 days, with an additional questionnaire at final follow-up. HF severity was scores as 1=mild, 2=moderate, 3=severe. The study notes that both groups experienced a decline in HF severity during the first month of study preparation. The differences between groups in severity at the end of the study were described as not statistically significant, and no additional data were provided.
Barton 1998	Vitamin E vs placebo (n=104 overall; crossover trial)	Diaries were used to measure HF's (including mean daily HF severity) during the baseline week and the two subsequent 4-week treatment periods. The authors suggest there were few to no benefits of Vitamin E for HF severity.

Sleep Function: Study Findings		
Study First Author and Year	Treatment Comparison	Findings
Comparisons Involving Pharmacologics		
Boekhout 2011	Venlafaxine (n=41) vs clonidine (n=41) vs placebo (n=20)	The Groningen Sleep Quality Scale (GSQ) was assessed. Sleep quality was not found to differ between the venlafaxine and clonidine intervention groups; no additional data or information was provided.
Biglia 2009	Gabapentin (n=60) vs vitamin E (n=55)	Based on findings from the PSQI, gabapentin demonstrated a statistically significant improvement in sleep quality from baseline; the gabapentin group incurred a mean global PSQI score reduction of 21.33% at twelve weeks and a mean absolute reduction of 1.67 (95% CI 0.90-2.43). The authors note that no significant change from baseline to twelve weeks was observed in women receiving Vitamin E. No numeric data for vitamin E is provided, nor is a statistical comparison between the gabapentin and vitamin E groups.
Stearns 2005	Paroxetine (2 dose levels; 10mg, 20mg)	The MOS Sleep Problems Index was assessed. All three intervention groups (placebo, paroxetine 10mg and paroxetine 20mg) were associated with improvements of at least

Sleep Function: Study Findings		
Study First Author and Year	Treatment Comparison	Findings
	vs placebo (crossover trial, n=151 overall)	10 points in the MOS Sleep Problems Index from baseline, however Paroxetine 10mg was associated with significantly greater improvement compared to placebo.
Comparisons Involving Non-Pharmacologics		
Bao 2014	Acupuncture (n=23) vs sham acupuncture (n=24)	Assessed sleep quality and sleep disturbance using Pittsburgh Sleep Quality Index (PSQI), which has both an overall score and seven domain scores (sleep quality; sleep latency; sleep duration; habitual sleep efficiency; sleep disturbance; use of sleeping medications; daytime dysfunction) which were summed to form a total score out of 21. Comparison of median and IQR scores between groups at 4, 8 and 12 weeks found no differences between acupuncture and sham acupuncture.
Chen 2014	Melatonin (n=48) vs placebo (n=47)	The authors observed significantly improved sleep quality in those taking melatonin compared to placebo in terms of PSQI global score as well as the sleep quality, sleep duration and daytime dysfunction sub-domains.
Mann 2012	CBT (n=47) vs usual care (n=49)	The sleep subscale of the Women's Health Questionnaire (WHQ) was assessed, with values ranging from 0-1 (lower values indicate better sleep). Women receiving CBT were found to demonstrate significantly fewer sleep problems at both 9 weeks (mean difference favouring CBT of -0.26, 95% CI -0.39 to -0.12) and 26 weeks (mean difference favouring CBT of -0.16, 95% CI -0.29 to -0.02) of follow-up compared to the usual care group.
Carson 2009	Yoga (n=17) vs waitlist (n=20)	Measured sleep disturbance on a scale from 0-9 (higher values denoted larger amounts). The yoga group was noted to have incurred significant post-treatment improvement in sleep disturbance compared to the control group (reduction from pre-treatment mean of 3.82 to 3.29 in the yoga group compared to pre- and post-treatment means of 4.21 and 4.37 in the control group; p < 0.01, but no 95% CI reported).
Elkins 2008	Hypnosis (n=27) vs waitlist (n=24)	The Medical Outcomes Study (MOS) Sleep Problems Index was assessed. Hypnosis was associated with an improvement in sleep compared to the control group after five weeks treatment (F-test from an analysis of covariance reported; p < 0.001), as well as in comparison to baseline levels within the group (MOS Sleep Index mean (SD) of 24.26 (8.17) at baseline and 13.71 (4.35) at follow-up).

Depression: Study Findings		
Study First Author and Year	Treatment Comparison	Findings
Comparisons Involving Pharmacologics		
Biglia 2016	Duloxetine (n=28) vs escitalopram (n=30)	Both the BDI and MADRS were evaluated. A significant reduction of depression from baseline was observed in both groups after both 4 and 12 weeks, with no important differences identified between treatments. In the duloxetine group, the mean MADRS score changed from 12.9 at baseline to 5.6 after 12 weeks (a 56.6% reduction), and BDI changed from 4.9 to 3.6 in the same time period (a 26.5% reduction). The corresponding changes in the escitalopram group were from 19.4 to 11.1 (a 42.8% reduction) for MADRS and from 8.3 to 6.6 (a 20.5% reduction) for BDI.
Boekhout 2011	Venlafaxine (n=41) vs clonidine (n=41) vs placebo (n=20)	The HADS tool was evaluated. After twelve weeks, depression scores were significantly higher in patients receiving venlafaxine than patients receiving clonidine (p=0.03), suggesting more depression. However, no additional numeric details are provided, and statistical comparisons with the placebo group are not detailed in the study report.
Walker 2010	Venlafaxine (n=25) vs acupuncture (n=25)	The Beck Depression Index Primary Care (BDI-PC) was evaluated. Both the venlafaxine group and the acupuncture group were associated with statistically significant reductions in depression after 12 months. The study report presents no detailed numeric data for changes within either group or the comparison of changes between groups; a figure within the report indicates overlapping confidence intervals at final follow-up, suggesting no statistically significant difference between groups was present. Digitized data from a study figure suggest reductions from 10.1 (SE 0.9) to 8.3 (SE 1.1) and from 12.1 (SE 0.8) to 9.6 (SE 1.1) in the venlafaxine group after twelve months.
Loprinzi 2009	Gabapentin (n=161 across 3 dose groups) vs placebo (n=54)	The POMS-B Scale was evaluated. At 4 weeks, no significant differences were identified between the gabapentin and placebo groups and its subdomains, which included depression/dejection. No additional numeric data are provided in the study report.
Kimmick 2006	Sertraline vs placebo (n=62 overall; crossover study)	The CES-D scale was evaluated. After 12 weeks, mean CES-D score increased in the sertraline group (from 11.2 (SD 9.2) to 12.8 (SD 11.7)) and decreased in the placebo group (from 11.5 (SD 7.9) to 7.9 (SD 6.8)). The study reports no important differences between groups with regard to effects on depression were identified.

Depression: Study Findings		
Study First Author and Year	Treatment Comparison	Findings
Stearns 2005	Paroxetine vs placebo (n=151 overall; crossover with 2 paroxetine groups)	The CES-D scale was evaluated. The study authors reported that after five weeks, there were no differences in the percentages of patients in the placebo and paroxetine groups who improved, worsened or stayed the same in terms of depressive symptoms.
Loprinzi 2000	Venlafaxine (n=165 across three dose groups) vs placebo (n=56)	The Beck Depression Inventory was evaluated (once per week for 5 weeks). The study authors reported that at the end of the study, totals of 16/48 (33% (evaluable patients in the placebo group, and corresponding totals of 11/40 (23%), 9/43 (21%) and 13/49 (27%) in the venlafaxine 37.5mg, 75mg and 150mg groups had depression scores consistent with the presence of at least mild depression.
Comparisons Involving Non-Pharmacologies		
Cramer 2015	Yoga (n=19) vs waitlist (n=21)	The HADS Scale was evaluated. No differences between the intervention groups for depression were observed at either 12 weeks (mean difference -0.70, 95% CI -1.7 to 0.3) or 24 weeks (mean difference 0.10, 95% CI -0.80 to 1.0). Changes from baseline were of small magnitude in both groups.
Stefanopoulou 2015	CBT (n=33) vs usual care (n=33)	The Hospital Anxiety and Depression Scale (HADS) was evaluated. No differences between the CBT and usual care groups were observed at either 6 weeks (adjusted mean difference -0.59, 95% CI -1.94 to 0.74) or 32 weeks (adjusted mean difference -0.52, 95% CI -1.15 to 2.20); point estimates favoured the CBT group.
Bao 2014	Acupuncture (n=23) vs sham acupuncture (n=24)	The Center for Epidemiologic Studies Depression (CES-D) Scale was evaluated. After eight weeks, reported median (IQR) changes in both the acupuncture group (reduction from median 16 (IQR of 9) at baseline to median 10 (IQR of 10.5)) and sham acupuncture group (reduction from median 10.5 (IQR of 10) at baseline to 6 (IQR of 11.25)) showed important changes within each group that reached statistical significance, while the difference between groups did not (p=0.44).
Chen 2014	Melatonin (n=48) vs placebo (n=47)	The CES-D Scale was evaluated. There was very little change in depression at four months from baseline in both the melatonin (mean change -0.2 (SD 4.6)) and placebo (mean change 0 (SD 5.4)) groups. No differences with respect to impact on depression were observed (p=0.66).

Depression: Study Findings		
Study First Author and Year	Treatment Comparison	Findings
Duijts 2012	CBT+exercise (n=106) vs exercise (n=104) vs CBT (n=109) vs control (n=103)	The HADS tool was evaluated. The authors note that after 6 months of treatment, no important differences in psychological distress/depression were observed between groups. The trial report provided no additional data to detail this summary.
Mann 2012	CBT (n=47) vs usual care (n=49)	The depression subscale of the Women's Health Questionnaire (WHQ) was evaluated. At 26 weeks of follow-up, the reduction in the CBT group (from mean 0.23 (SD 0.16) to mean 0.13 (SD 0.19)) was found to be significantly greater than the change in the usual care group (from mean 0.31 (SD 0.27) to 0.28 (SD 0.26)); mean difference - 0.13, 95% CI -0.22 to -0.05. A very similar difference was also present earlier on, at 9 weeks.
Elkins 2008	Hypnosis (n=27) vs waitlist (n=24)	The CES-D scale was evaluated. Data suggested an important mean reduction in the hypnosis group (from 29.48 (SD 7.72) to 24.58 (SD 6.45)) compared to the waitlist group (from 30.22 (SD 9.32) to 31.38 (SD 9.21)). The difference between groups was statistically significant in favour of the hypnosis group (p<0.01).
Jacobson 2001	Black cohosh (n=42) vs placebo (n=43)	The study reports evaluating changes in several menopausal symptoms, one of which was depression, though further details are not provided with regard to approach to measurement. The article denotes that while symptoms in general improved in both groups, there were no changes that were specifically impacted by treatment.

Sexual Function: Study Findings		
Study First Author and Year	Treatment Comparison	Findings
Comparisons Involving Pharmacologics		
Boekhout 2011	Venlafaxine (n=41) vs clonidine (n=41) vs placebo (n=20)	Looked at changes in the overall Sexual Activity Questionnaire (SAQ). The authors report there were no important differences noted for sexual function between the intervention groups; no detailed numeric data are provided to give further insights.
Stearns 2005	Paroxetine vs placebo (n=151 overall)	Looked at the Medical Outcomes Study (MOS) Sexual Problems Index. The study authors report that the following numbers of patients improved / stayed the same /

Sexual Function: Study Findings		
Study First Author and Year	Treatment Comparison	Findings
		worsened: Placebo = 9 (25%) / 21 (58%) / 6 (17%); Paroxetine 10mg = 3 (20%) / 10 (67%) / 2 (13%); Paroxetine 20mg = 4 (25%) / 7 (44%) / 5 (31%). Thus, there were no important gains associated with paroxetine.
Loprinzi 2002	Fluoxetine vs placebo (n=81 overall)	Looked at libido change based on element 21 of the Beck Depression Index. The study report noted that after five weeks of treatment, totals of 11 patients in the fluoxetine group and 9 in the placebo group had improved libido compared to baseline, while totals of 1 patient in the fluoxetine group and 3 in the placebo group had reduced libido compared to baseline. Fluoxetine thus appeared to offer some gains, though no formal statistical comparisons were performed.
Loprinzi 2000	Venlafaxine (n=165 across three dose groups) vs placebo (n=56)	Looked at libido change based on element 21 of the Beck Depression Index. Improvements in libido were observed in the placebo group as well as patients receiving all doses of venlafaxine, however the authors do not report formal statistical comparisons to establish statistical significance nor clinical relevance of the between-group differences. Numeric values are also unreported, with only a line graph presented (one profile per group).
Comparisons Involving Non-Pharmacologics		
Duijts 2012	CBT+exercise (n=106) vs exercise (n=104) vs CBT (n=109) vs waitlist (n=103)	Looked at both the Habit and Pleasure subscales of the Sexual Activity Questionnaire (SAQ). Data analyses identified a statistically significant improvement in sexual function (SAQ-Habit) in the CBT + exercise group compared to the control group at long-term follow-up (effect size 0.65, p=0.002). Supplemental per protocol analyses also identified important gains in SAQ-Pleasure in the CBT and CBT+exercise groups.

Generic Quality of Life: Findings			
Study First Author and Year	Time of assessment	Treatments compared	Findings
Cramer 2015	24 wks	Waitlist vs yoga	FACT-B was significantly different at 24 weeks in regard to total score (group difference 12.6, 95% CI 4.2 to 21.1 in favour of yoga), as well as the physical

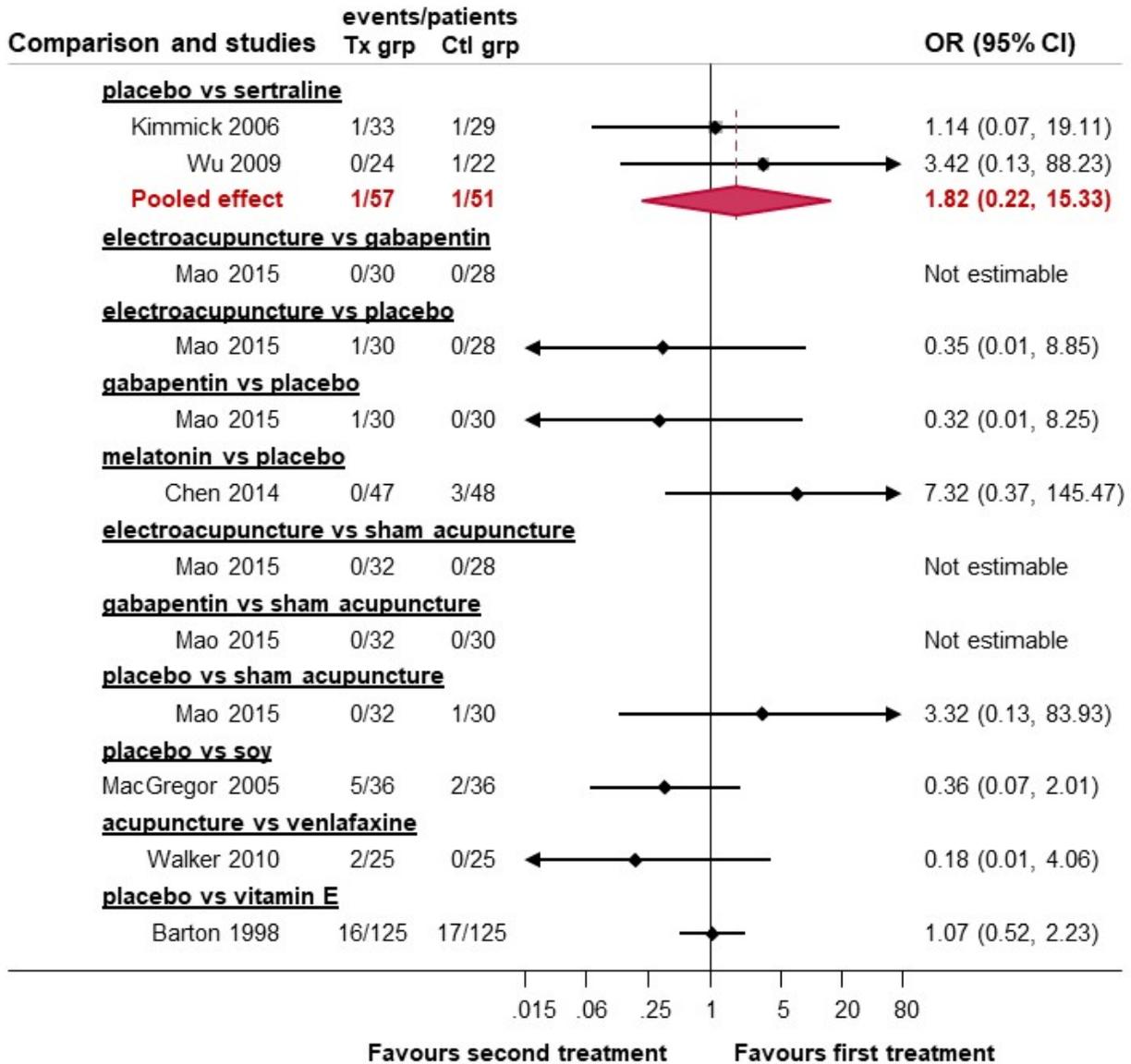
Generic Quality of Life: Findings			
Study First Author and Year	Time of assessment	Treatments compared	Findings
			(between group difference 3.6, 95% CI 0.9 to 6.3 in favour of yoga), social (between group difference 2.6, 95% CI 0.5 to 4.7) and emotional well being (between group difference, 95% CI 1.6, 95% CI 0.1 to 3.1) subscales.
Stefanopoulou 2015	32 wks	Usual care vs CBT	There was no difference in EORTC QLQ-C30 at either 6 weeks (3.61, 95% CI -5.41 to 12.63) or 32 weeks (95% CI -0.97, 95% CI -13.01 to 11.01).
Bao 2014	8 wks	Sham acupuncture vs acupuncture	At 12 weeks, median and IQR values of EuroQoL in both groups were equivalent (median 80, IQR 20).
Vitolins 2013	12 wks	Venlafaxine vs soy	The authors reported there were no significant effects of venlafaxine on FACT-P, FACT-G or subscales (social, emotional, physical, functional, prostate) after twelve weeks of follow-up in both unadjusted and adjusted analyses. In patients receiving soy (compared to those not receiving soy), there were important differences in FACT-G scores, FACT-P scores and in the related emotional and functional domains.
Bordeleau 2010	4 wks	Gabapentin vs venlafaxine	After four weeks, no differences between interventions were observed (detailed data not reported).
Walker 2010	64 wks	Acupuncture vs venlafaxine	There were no significant differences between intervention groups after 12 weeks (numeric details reported only in graphical format)
Biglia 2009	12 wks	Gabapentin vs vitamin E	Analysis of SD-36 data showed that mild improvements in health related quality of life with gabapentin: statistically significant changes were noted in both the mental health (absolute change -8.32, 95% CI -13.78 to -2.86) and physical health (absolute change -6.53, 95% CI -12.12 to -0.92) components. Changes did not reach significance in the Vitamin E group (data not reported).
Wu 2009	6 wks	Placebo vs sertraline	after 6 weeks, emotional well being was associated with a significantly greater improvement in emotional well being compared to placebo (p=0.041), however changes in physical, social/family and functional well being were not significant (all p>0.05). Only 39 of 46 randomized patients were included in the analyses.

Generic Quality of Life: Findings			
Study First Author and Year	Time of assessment	Treatments compared	Findings
Loprinzi 2009	4 wks	Placebo vs gabapentin	Changes in QoL (measured on a 10-point scale) after 4 weeks showed no significant difference between the placebo and gabapentin groups.
Fenlon 2008	13 wks	No trt vs relaxation	Comparison of median change in quality of life measured using the FACT-ES scale found no difference between the relaxation and no treatment groups (median difference 0.12, 95% CI -4.06 to 4.65).
Loprinzi 2007	4 wks	Gabapentin vs gabapentin+antidepressant	The study authors reported that there were no significant differences between groups in changes in linear analog self-assessment quality-of-life measures from baseline to week 4 for overall quality of life (P = .98) or for the related subdomains of mental well-being (P = .27), physical well-being (P = .23), emotional well-being (P = .45), social activity (P = .82), or spiritual well-being (P = .77).
Kimmick 2006	6 wks	Placebo vs sertraline	There were no important differences in changes in quality of life between groups from baseline levels (placebo: mean (SD) 122.1 (14.4) vs sertraline: 119.4 (18.7)) after either 6 weeks (placebo: 120.6 (12.3) vs sertraline: 126.4 (19.7); p=0.32) or 12 weeks (placebo: 124.2 (15.5) vs sertraline: 117.0 (18.5); p=0.88) of follow-up.
MacGregor 2005	12 wks	Placebo vs soy	Comparison of EORTC QLQ30 findings (range 0-100) between groups at 12 weeks found no difference (p=0.844).
Nedstrand 2005	38 wks	Relaxation vs electroacupuncture	There were improvements in psychological well being (as measured by the Symptom Checklist) in both the relaxation and electroacupuncture groups at 12 weeks; the differences between groups were not statistically significant. Statistically significant improvement in mood after 12 weeks was only observed in the electroacupuncture group.
Stearns 2005	4 wks	Placebo vs sertraline	Study authors reported that after 4 weeks, the proportions of patients maintaining and improving their quality of life status based on the EuroQoL linear rating scale were similar in all treatment groups.
Loprinzi 2002	4 wks	Placebo vs fluoxetine	There was insufficient evidence of an importance difference in patients' global rating of health and well being scores (range 0-100) to suggest the presence of an important difference between fluoxetine and placebo.

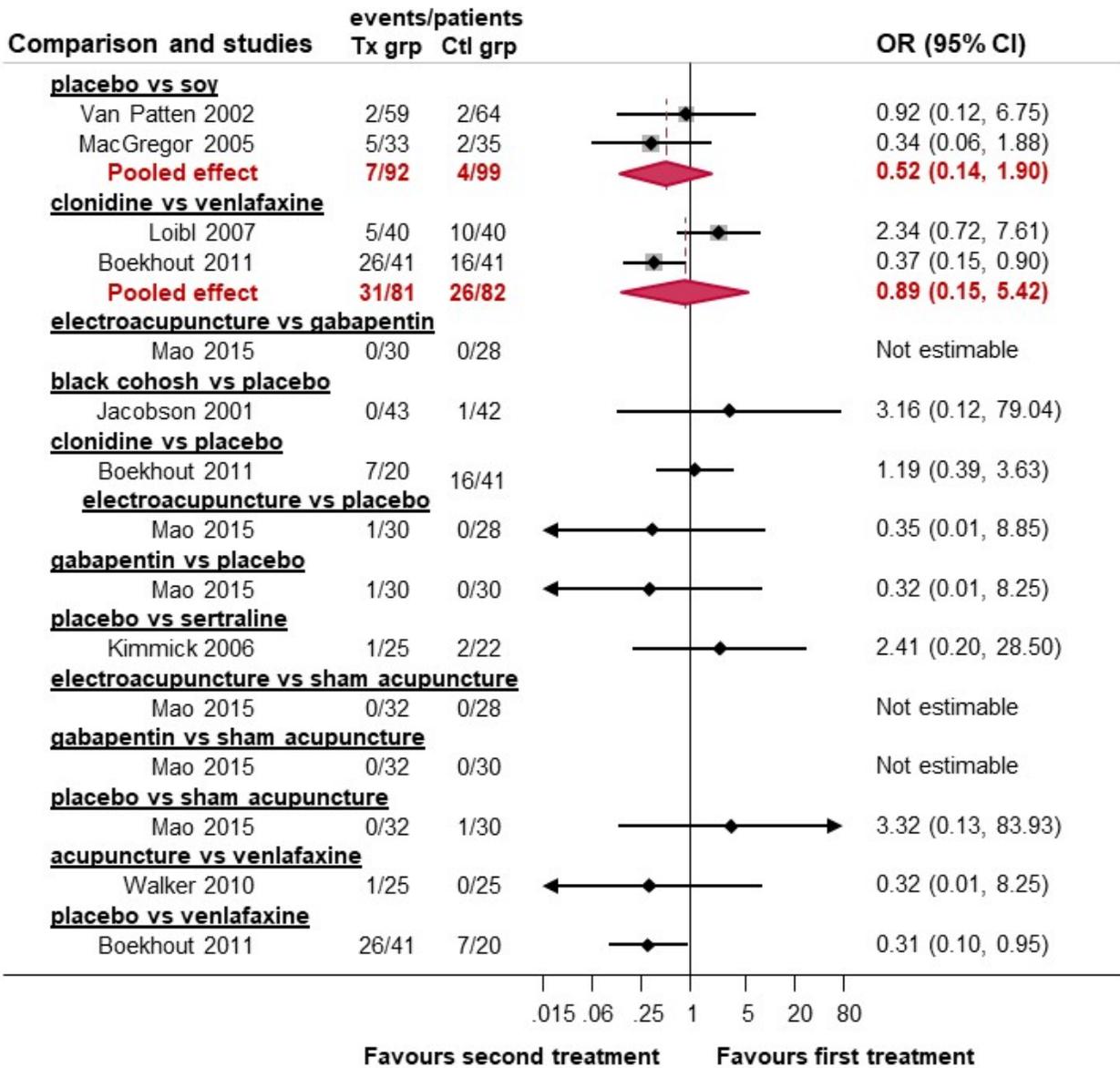
Generic Quality of Life: Findings			
Study First Author and Year	Time of assessment	Treatments compared	Findings
Jacobson 2001	9 wks	Placebo vs black cohosh	The authors reported that there were no important changes in the global rating of health and well being in either treatment group (additional data were not provided).
Loprinzi 2000	4 wks	Placebo vs venlafaxine	Based upon a single item quality of life question, after 4 weeks the study authors observed an average 3-point improvement in the venlafaxine groups and a 3-point reduction in the placebo group (p=0.02) based upon a single-item QoL tool.
Pandya 2000	12 wks	Placebo vs clonidine	Based on quality of life assessments rated on a scale from 1-10, differences after 4 and 8 weeks of follow-up showed a statistically significant difference between groups favoring clonidine over placebo. At 12 weeks, the difference was no longer statistically significant.

Tolerability Data: Constipation, Headache, Fatigue, Nausea

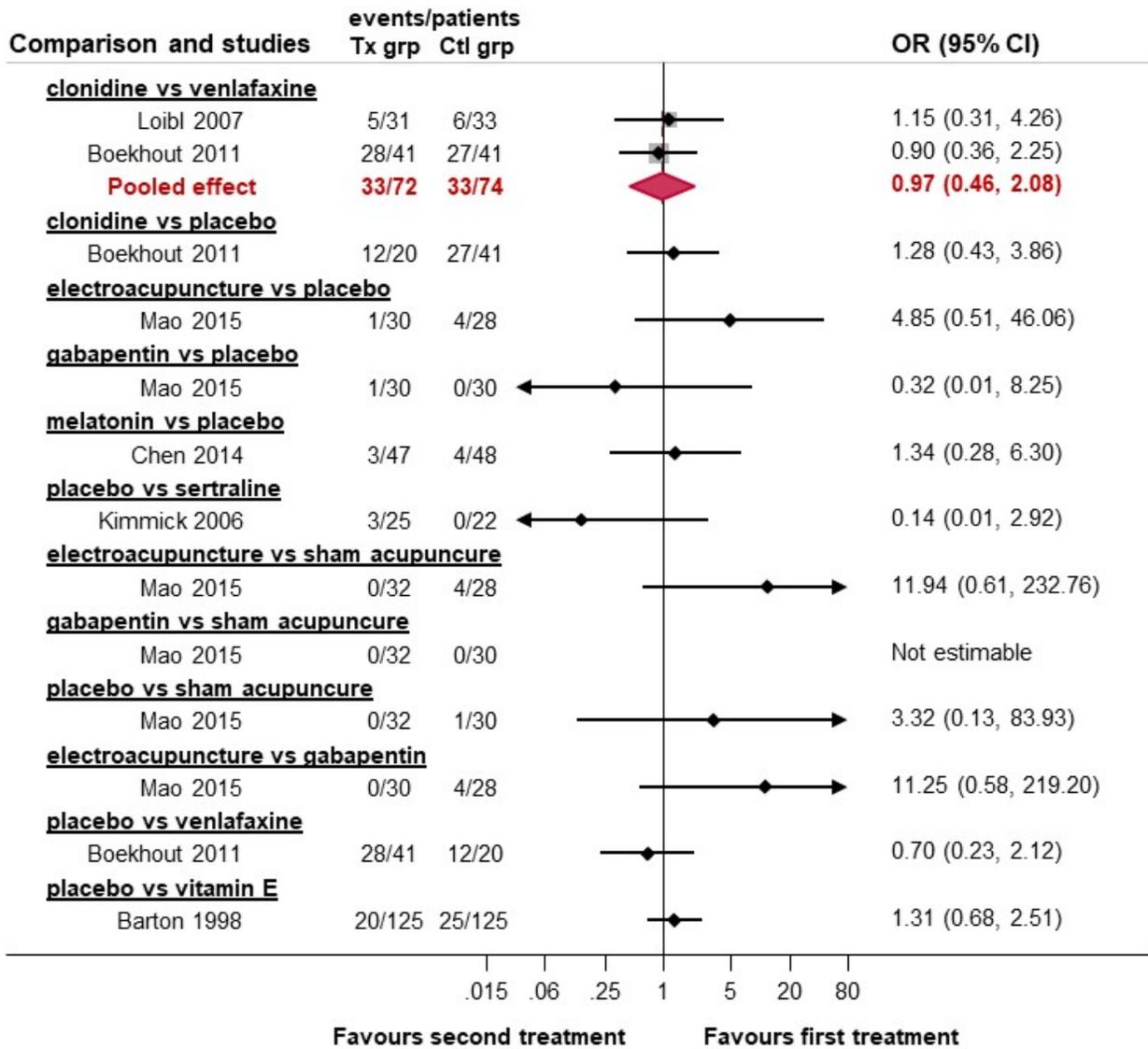
Headache:



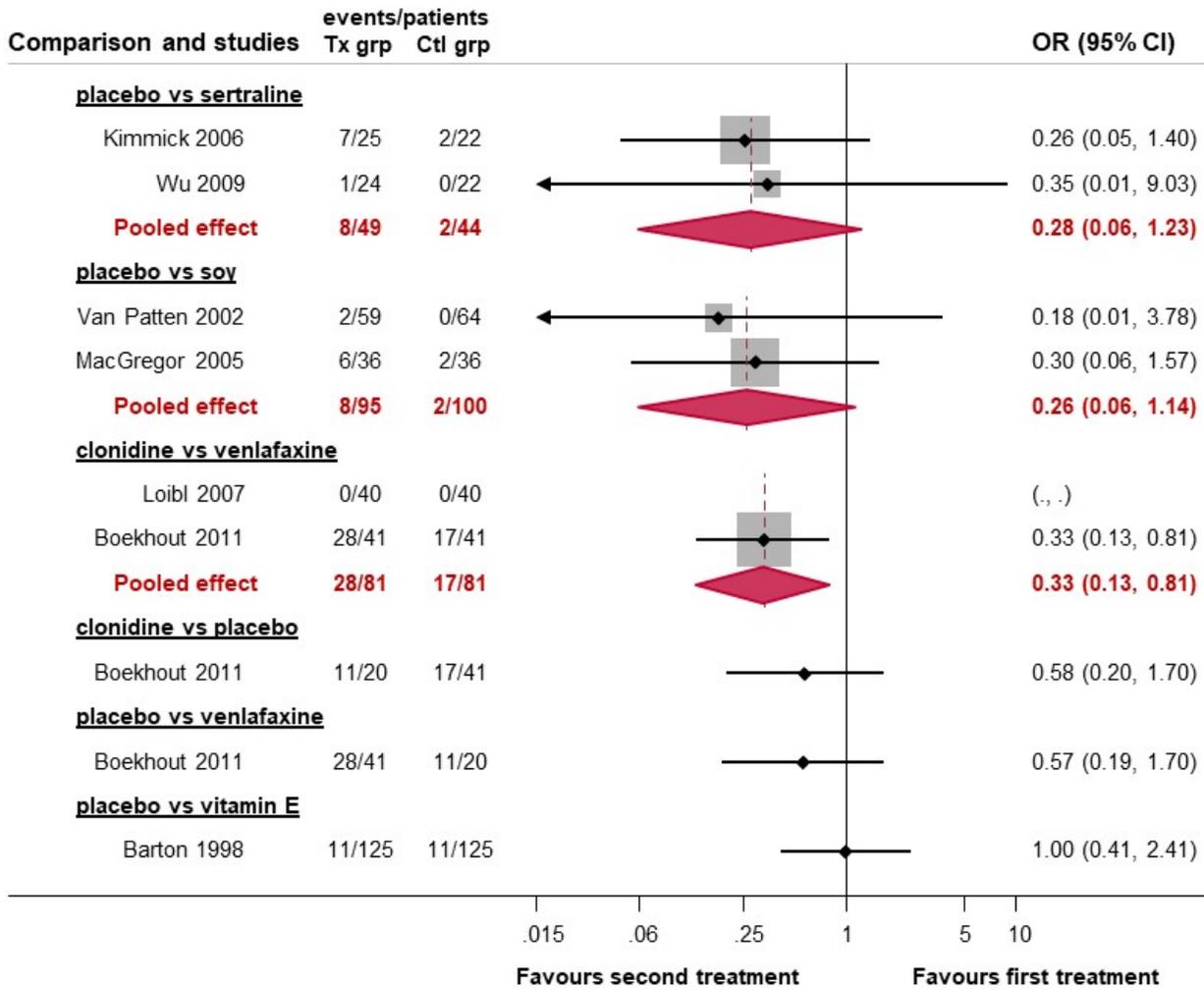
Constipation:



Fatigue:



Nausea:



Appendix 12: Overview of GRADE Certainty of Evidence

The following table presents the results of the graded network meta-analysis comparing each active intervention to placebo for the outcomes of hot flash composite score and hot flash frequency.

Primary Outcomes	CoE	Classification	Intervention	RoM (95% CI) vs PLC
Hot flash composite score	Low (Low to very low)	May be among the most effective	Venlafaxine	1.71 (1.05, 2.76)
			Paroxetine	2.83 (1.31, 6.09)
			Clonidine	2.13 (1.27, 3.54)
			Electroacupuncture	2.07 (1.01, 4.24)
		May be no more effective than placebo	Gabapentin	1.43 (0.95, 2.12)
			Gabapentin + Antidepressants	1.34 (0.59, 3.01)
			Sertraline	1.58 (0.70, 3.41)
			Sham acupuncture	1.65 (0.83, 3.31)
			Melatonin	0.70 (0.05, 11.19)
		May be among the least effective	Vitamin E	0.14 (0.03, 0.58)
Hot flash frequency	High (Moderate to High)	Among the most effective	Venlafaxine	2.48 (1.36, 4.32)
		No more effective than placebo	Gabapentin	1.62 (0.92, 2.73)
	Low (Low to very low)	May be among the most effective	Paroxetine	3.15 (1.29, 7.58)
		May be among the least effective	Clonidine	1.62 (0.86, 2.98)
			Gabapentin + Antidepressants	1.80 (0.65, 4.65)
			Sertraline	1.67 (0.69, 3.94)
			Melatonin	1.03 (0.11, 8.90)
Vitamin E	0.27 (0.06, 1.18)			

*CI: Confidence interval; CoE: Certainty of evidence; RoM: Ratio of Means (e.g. mean reduction of HF frequency in intervention / mean reduction of HF frequency in placebo)

Appendix 13: PRISMA NMA Checklist

PRISMA NMA Checklist of Items to Include When Reporting a Systematic Review Involving a Network Meta-analysis

Section/Topic	Item #	Checklist Item	Reported on Page #
TITLE			
Title	1	Identify the report as a systematic review <i>incorporating a network meta-analysis (or related form of meta-analysis)</i> .	1
ABSTRACT			
Structured summary	2	Provide a structured summary including, as applicable: Background: main objectives Methods: data sources; study eligibility criteria, participants, and interventions; study appraisal; and <i>synthesis methods, such as network meta-analysis</i> . Results: number of studies and participants identified; summary estimates with corresponding confidence/credible intervals; <i>treatment rankings may also be discussed</i> . <i>Authors may choose to summarize pairwise comparisons against a chosen treatment included in their analyses for brevity.</i> Discussion/Conclusions: limitations; conclusions and implications of findings. Other: primary source of funding; systematic review registration number with registry name.	1
INTRODUCTION			
Rationale	3	Describe the rationale for the review in the context of what is already known, <i>including mention of why a network meta-analysis has been conducted</i> .	1-2
Objectives	4	Provide an explicit statement of questions being addressed, with reference to participants, interventions, comparisons, outcomes, and study design (PICOS).	2
METHODS			
Protocol and registration	5	Indicate whether a review protocol exists and if and where it can be accessed (e.g., Web address); and, if available, provide registration information, including registration number.	2
Eligibility criteria	6	Specify study characteristics (e.g., PICOS, length of follow-up) and report characteristics (e.g., years considered, language, publication status) used as criteria for eligibility, giving rationale. <i>Clearly describe eligible treatments included in the treatment network, and note whether any have been clustered or merged into the same node (with justification)</i> .	2-3; Appendix 2
Information sources	7	Describe all information sources (e.g., databases with dates of coverage, contact with study authors to identify additional studies) in the search and date last searched.	2

Search	8	Present full electronic search strategy for at least one database, including any limits used, such that it could be repeated.	Appendix 1
Study selection	9	State the process for selecting studies (i.e., screening, eligibility, included in systematic review, and, if applicable, included in the meta-analysis).	3
Data collection process	10	Describe method of data extraction from reports (e.g., piloted forms, independently, in duplicate) and any processes for obtaining and confirming data from investigators.	3
Data items	11	List and define all variables for which data were sought (e.g., PICOS, funding sources) and any assumptions and simplifications made.	3
Geometry of the network	S1	Describe methods used to explore the geometry of the treatment network under study and potential biases related to it. This should include how the evidence base has been graphically summarized for presentation, and what characteristics were compiled and used to describe the evidence base to readers.	3-4
Risk of bias within individual studies	12	Describe methods used for assessing risk of bias of individual studies (including specification of whether this was done at the study or outcome level), and how this information is to be used in any data synthesis.	3
Summary measures	13	State the principal summary measures (e.g., risk ratio, difference in means). <i>Also describe the use of additional summary measures assessed, such as treatment rankings and surface under the cumulative ranking curve (SUCRA) values, as well as modified approaches used to present summary findings from meta-analyses.</i>	3-4
Planned methods of analysis	14	Describe the methods of handling data and combining results of studies for each network meta-analysis. This should include, but not be limited to: <ul style="list-style-type: none"> • <i>Handling of multi-arm trials;</i> • <i>Selection of variance structure;</i> • <i>Selection of prior distributions in Bayesian analyses;</i> and • <i>Assessment of model fit.</i> 	3-4
Assessment of Inconsistency	S2	Describe the statistical methods used to evaluate the agreement of direct and indirect evidence in the treatment network(s) studied. Describe efforts taken to address its presence when found.	3-4
Risk of bias across studies	15	Specify any assessment of risk of bias that may affect the cumulative evidence (e.g., publication bias, selective reporting within studies).	NA
Additional analyses	16	Describe methods of additional analyses if done, indicating which were pre-specified. This may include, but not be limited to, the following:	3-4

- Sensitivity or subgroup analyses;
- Meta-regression analyses;
- *Alternative formulations of the treatment network; and*
- *Use of alternative prior distributions for Bayesian analyses (if applicable).*

RESULTS†

Study selection	17	Give numbers of studies screened, assessed for eligibility, and included in the review, with reasons for exclusions at each stage, ideally with a flow diagram.	4; Appendix 2
Presentation of network structure	S3	Provide a network graph of the included studies to enable visualization of the geometry of the treatment network.	Figures 1, 2
Summary of network geometry	S4	Provide a brief overview of characteristics of the treatment network. This may include commentary on the abundance of trials and randomized patients for the different interventions and pairwise comparisons in the network, gaps of evidence in the treatment network, and potential biases reflected by the network structure.	7-8; Figures 1, 2
Study characteristics	18	For each study, present characteristics for which data were extracted (e.g., study size, PICOS, follow-up period) and provide the citations.	4-9; Table 1
Risk of bias within studies	19	Present data on risk of bias of each study and, if available, any outcome level assessment.	Appendix 7
Results of individual studies	20	For all outcomes considered (benefits or harms), present, for each study: 1) simple summary data for each intervention group, and 2) effect estimates and confidence intervals. <i>Modified approaches may be needed to deal with information from larger networks.</i>	Data supplement file
Synthesis of results	21	Present results of each meta-analysis done, including confidence/credible intervals. <i>In larger networks, authors may focus on comparisons versus a particular comparator (e.g. placebo or standard care), with full findings presented in an appendix. League tables and forest plots may be considered to summarize pairwise comparisons.</i> If additional summary measures were explored (such as treatment rankings), these should also be presented.	9-15
Exploration for inconsistency	S5	Describe results from investigations of inconsistency. This may include such information as measures of model fit to compare consistency and inconsistency models, <i>P</i> values from statistical tests, or summary of inconsistency estimates from different parts of the treatment network.	Appendices 8, 9
Risk of bias across studies	22	Present results of any assessment of risk of bias across studies for the evidence base being studied.	NA
Results of additional analyses	23	Give results of additional analyses, if done (e.g., sensitivity or subgroup analyses, meta-regression analyses, <i>alternative network geometries studied, alternative choice of prior distributions for Bayesian analyses, and so forth</i>).	Not feasible

DISCUSSION

Summary of evidence	24	Summarize the main findings, including the strength of evidence for each main outcome; consider their relevance to key groups (e.g., healthcare providers, users, and policy-makers).	15-16
Limitations	25	Discuss limitations at study and outcome level (e.g., risk of bias), and at review level (e.g., incomplete retrieval of identified research, reporting bias). <i>Comment on the validity of the assumptions, such as transitivity and consistency. Comment on any concerns regarding network geometry (e.g., avoidance of certain comparisons).</i>	16-17
Conclusions	26	Provide a general interpretation of the results in the context of other evidence, and implications for future research.	17
FUNDING			
Funding	27	Describe sources of funding for the systematic review and other support (e.g., supply of data); role of funders for the systematic review. This should also include information regarding whether funding has been received from manufacturers of treatments in the network and/or whether some of the authors are content experts with professional conflicts of interest that could affect use of treatments in the network.	17

PICOS = population, intervention, comparators, outcomes, study design.

* Text in italics indicates wording specific to reporting of network meta-analyses that has been added to guidance from the PRISMA statement.

† Authors may wish to plan for use of appendices to present all relevant information in full detail for items in this section.