Network meta-analysis of HAMA

Version 2022.07.21

Content

METHODS

Data management

From the dataset '*NKA_beroligend_NMA_treatment_19.05.2022_SMN_KM220622_au15.07.22*', received 15/7-2022, the variables used in the network meta-analysis are Author, MD_{HAMA}, SD_{HAMA}, n_{HAMA}, as well as SMC_{HAMA}, and $SE(SMC_{HAMA})$, calculated from $SMC_{HAMA} = MD_{HAMA} / SD_{HAMA}$, and $SE(SMC_{HAMA}) = \sqrt{(1/n_{HAMA} + SMC_{HAMA}^2 /(2*n_{HAMA}))}$. For the CINeMA assessment, the variables RoB, Indirectness, and Reporting_bias were used, and for evaluating transitivity, Diagnosis, Co-medication_randomised, Placebo_run_in, were used.

Trials testing the same drug in multiple arms (but in different doses), were handled by pooling those arms. Hence, individual trials contribute only a single arm for a specific treatment. This should be kept in mind when looking at the summarized number of arms pr. trial and the number of comparisons included in the analysis.

Analysis

We performed a random-effects network meta-analysis as the primary analysis. We estimated the standardized mean difference (SMD) with corresponding confidence intervals for each treatment comparison, and we evaluated the rank probabilities and estimated the p-scores. For the CINeMA assessments (incl. the domains within-study bias, reporting bias, indirectness, imprecision, heterogeneity, and incoherence), it was decided to only evaluate the comparisons between the treatments ***Benzodiazepin, placebo, Mianserin, Pregabalin, Quetiapin, Hydroxin, and Agomelatin***.

For sensitivity, we performed a Bayesian random-effects network meta-analysis using Markov-chain Monte-Carlo simulation with vague priors. We evaluated the ranking probabilities and calculated the surface under the cumulative ranking curves (SUCRA). We assessed the convergence based on trace plots and the Gelman-Rubin statistic.

The transitivity assumption underlying network meta-analysis (i.e., that the network includes studies that are sufficiently similar in important clinical and methodological characteristics [potential effect modifiers]) was evaluated by comparing the distribution of clinical and methodological variables that could act as effect modifiers across treatment comparisons, as well as conceptually evaluating the definition of each node (treatment) in the network, and that the treatments have similar indications (i.e., are in principle jointly randomizable). We evaluated the consistency (i.e., the agreement between direct and indirect evidence; sometimes called coherence) by considering direct and indirect evidence separately with node splitting (also called side-splitting).

The network meta-analyses were performed in R version 4.0.3 (R Core Team, Vienna, Austria) with the *netmeta* and *gemtc* packages, of which the latter performs network meta-analyses within the Bayesian framework using JAGS (i.e., a program for analysis of Bayesian hierarchical models using Markov-chain Monte-Carlo simulation). The *pcnetmeta* package was used to draw the network plots. For the CINeMA assessment, we used the CINeMA software (cinema.ispm.unibe.ch).

Regarding transitivity, PRISMA-NMA states:

"Methods for indirect treatment comparisons and network meta-analysis enable learning about the relative treatment effects of, for example, treatments A and B through use of studies where these interventions are compared against a common therapy, C.

When planning a network meta-analysis, it is important to assess patient and study characteristics across the studies that compare pairs of treatments. These characteristics are commonly referred to as effect modifiers and include such traits as average patient age, gender distribution, disease severity, and a wide range of other plausible features.

For network meta-analysis to produce valid results, it is important that the distribution of effect modifiers is similar, for example, across studies of A versus B and A versus C. This balance increases the plausibility of reliable findings from an indirect comparison of B versus C through the common comparator A. When this balance is present, the assumption of transitivity can be judged to hold.

Authors of network meta-analyses should present systematic (and even tabulated) information regarding patient and study characteristics whenever available. This information helps readers to empirically evaluate the validity of the assumption of transitivity by reviewing the distribution of potential effect modifiers across trials."
Hutton et al. The PRISMA Extension Statement for Reporting of Systematic Reviews Incorporating Network Meta-analyses of Health Care Interventions: Checklist and Explanations. Ann Intern Med. 2015;162(11):777-784.

Regarding consistency, PRISMA-NMA states:
"Network meta-analysis often involves the combination of direct and indirect evidence. In the simplest case, we wish to compare treatments A and B and have 2 sources of information: direct evidence via studies comparing A versus B, and indirect evidence via groups of studies comparing A and B with a common intervention, C. Together, this evidence forms a closed loop, ABC. Direct and indirect evidence for a comparison of interventions should be combined only when their findings are similar in magnitude and interpretation. For example, for a comparison of mortality rates between A and B, an odds ratio determined from studies of A versus B should be similar to the odds ratio comparing A versus B estimated indirectly based on studies of A versus C and B versus C. This assumption of comparability of direct and indirect evidence is referred to as consistency of treatment effects. When a treatment network contains a closed loop of interventions, it is possible to examine statistically whether there is agreement between the direct and indirect estimates of intervention effect. (…) Inconsistency in a treatment network can indicate lack of transitivity."
Hutton et al. The PRISMA Extension Statement for Reporting of Systematic Reviews Incorporating Network Meta-analyses of Health Care Interventions: Checklist and Explanations. Ann Intern Med. 2015;162(11):777-784.

RESULTS

A total of **31** trials investigating **19** different treatments in **77** treatment arms, contributing with **61** direct comparisons, were included in the network meta-analysis on HAMA

Figure 1: Flow diagram
(pending SST)

Table 1: Trial characteristics
(pending SST)

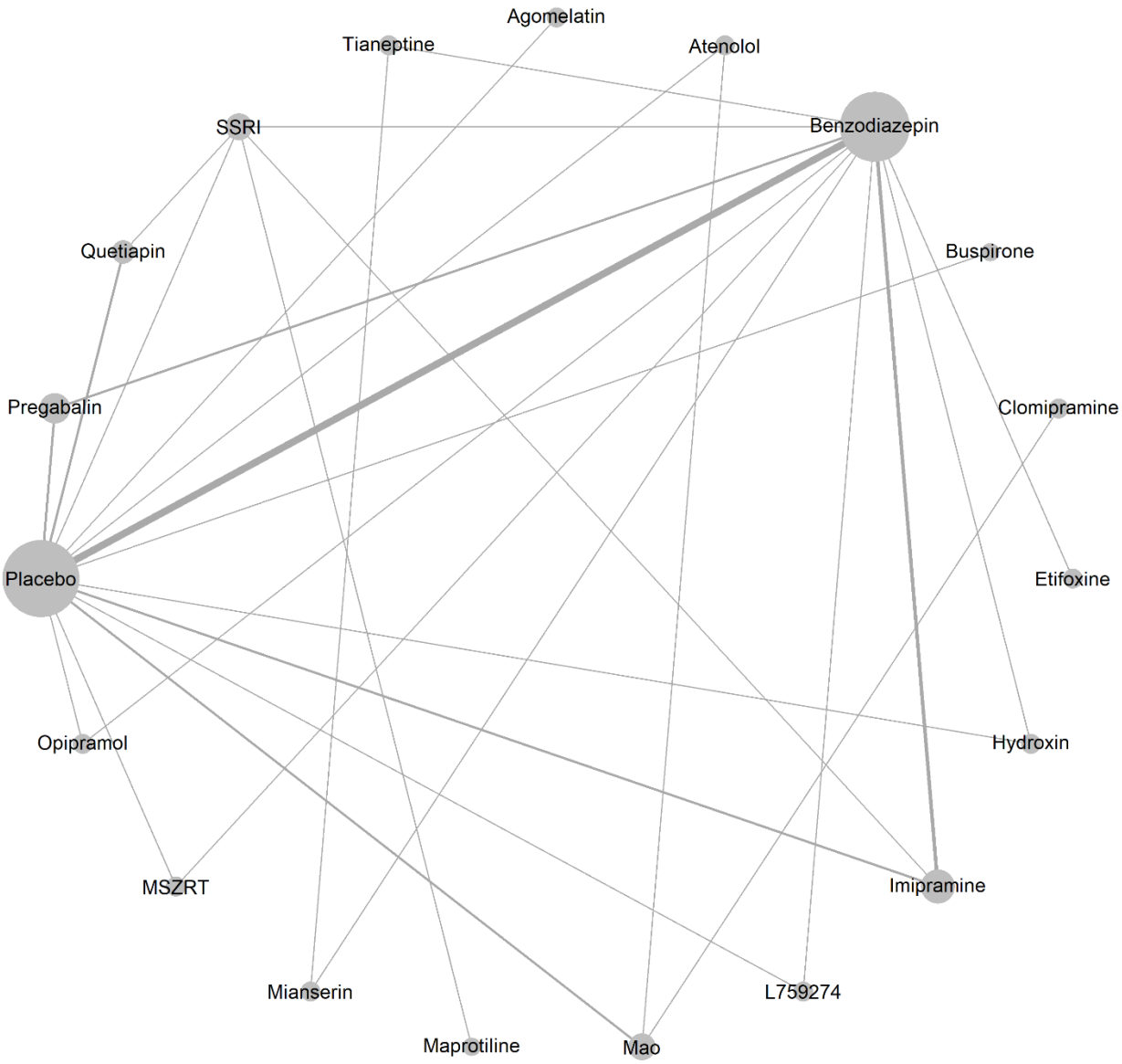


Figure 2: Network plot

The circle size reflects the number of trials, and the line width reflects the number of comparisons. No connecting line between two treatments indicates that there is no direct comparison.

Table 2: Description of network

Table 2-A: Number of n-arm trials

n-arm	No. trials
2-arm	16
3-arm	15

(The sum is 31 trials)

Table 2-B: Trials per treatment

Treatment	No. trials
Benzodiazepin	18
Imipramine	6
Placebo	22
SSRI	4
Tianeptine	1
Mianserin	1
Clomipramine	2
Mao	5
Maprotiline	1
Pregabalin	4
Quetiapin	3
Atenolol	1
Hydroxin	1
L759274	1
Opipramol	1
Etifoxine	2
MSZRT	1
Agomelatin	2
Buspirone	1

(There are 19 different treatments; The sum is 77 treatment arms across the 31 trials)

Table 2-C: Trials per treatment comparison

Treatment 1	Treatment 2	No. trials
Benzodiazepin	Imipramine	5
Benzodiazepin	Placebo	13
Benzodiazepin	SSRI	1
Benzodiazepin	Tianeptine	1
Benzodiazepin	Mianserin	1
Benzodiazepin	Pregabalin	4
Benzodiazepin	Hydroxin	1
Benzodiazepin	L759274	1
Benzodiazepin	Opipramol	1
Benzodiazepin	Etifoxine	2
Benzodiazepin	MSZRT	1
Imipramine	Placebo	3
Imipramine	SSRI	2
Placebo	SSRI	1
Placebo	Pregabalin	4
Placebo	Quetiapin	3
Mianserin	Tianeptine	1
Clomipramine	Mao	2
Mao	Placebo	3
Maprotiline	SSRI	1
Quetiapin	SSRI	1
Atenolol	Placebo	1
Atenolol	Mao	1
Hydroxin	Placebo	1
L759274	Placebo	1
Opipramol	Placebo	1
MSZRT	Placebo	1
Agomelatin	Placebo	2
Buspirone	Placebo	1

(There are 29 different comparisons; The sum is 61 direct comparisons; 16 2-arm and 15 3-arm trials contribute with 16+3*15 = 61 comparisons in total)

Table 3: Results for all treatment comparisons (SMDs with 95%CIs)

Agomelatin	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	-0.22 (-0.67; 0.24)
0.07 (-0.81; 0.95)	Atenolol	.	.	.	.	.	.	.	0.06 (-0.76; 0.89)	.	.	.	.	.	.	.	.	-0.19 (-1.00; 0.62)
0.37 (-0.12; 0.86)	0.30 (-0.47; 1.07)	Benzodiazepin	.	.	-0.25 (-0.71; 0.21)	-0.19 (-0.83; 0.45)	-0.93 (-1.26; -0.59)	-0.41 (-1.08; 0.27)	.	.	-0.14 (-0.84; 0.56)	-0.18 (-0.88; 0.53)	0.08 (-0.56; 0.72)	0.05 (-0.28; 0.37)	.	-0.68 (-1.47; 0.12)	-0.23 (-0.93; 0.47)	-0.60 (-0.79; -0.41)
-0.07 (-1.10; 0.96)	-0.14 (-1.33; 1.05)	-0.44 (-1.38; 0.51)	Buspirone	.	.	.	.	.	.	.	.	.	.	.	.	.	.	-0.15 (-1.07; 0.77)
0.69 (-0.14; 1.51)	0.62 (-0.28; 1.52)	0.32 (-0.39; 1.03)	0.75 (-0.40; 1.91)	Clomipramine	.	.	.	.	-0.45 (-0.94; 0.04)	.	.	.	.	.	.	.	.	.
0.12 (-0.56; 0.79)	0.05 (-0.85; 0.94)	-0.25 (-0.71; 0.21)	0.18 (-0.86; 1.23)	-0.57 (-1.42; 0.28)	Etifoxine	.	.	.	.	.	.	.	.	.	.	.	.	.
0.09 (-0.64; 0.81)	0.01 (-0.92; 0.95)	-0.28 (-0.85; 0.28)	0.15 (-0.93; 1.23)	-0.60 (-1.49; 0.29)	-0.03 (-0.76; 0.70)	Hydroxin	.	.	.	.	.	.	.	.	.	.	.	-0.21 (-0.85; 0.43)
-0.47 (-1.03; 0.08)	-0.55 (-1.36; 0.27)	-0.84 (-1.15; -0.54)	-0.41 (-1.38; 0.57)	-1.16 (-1.92; -0.41)	-0.59 (-1.14; -0.04)	-0.56 (-1.19; 0.07)	Imipramine	.	.	.	.	.	.	.	.	0.49 (-0.12; 1.10)	.	0.22 (-0.19; 0.64)
-0.01 (-0.76; 0.74)	-0.08 (-1.03; 0.87)	-0.38 (-0.97; 0.21)	0.06 (-1.04; 1.15)	-0.70 (-1.60; 0.21)	-0.13 (-0.87; 0.62)	-0.10 (-0.90; 0.71)	0.47 (-0.19; 1.12)	L759274	.	.	.	.	.	.	.	.	.	-0.23 (-0.91; 0.44)
0.24 (-0.42; 0.90)	0.17 (-0.59; 0.92)	-0.13 (-0.64; 0.38)	0.30 (-0.74; 1.34)	-0.45 (-0.94; 0.04)	0.12 (-0.57; 0.81)	0.15 (-0.59; 0.89)	0.71 (0.14; 1.28)	0.25 (-0.51; 1.01)	Mao	.	.	.	.	.	.	.	.	-0.45 (-0.93; 0.02)
0.14 (-0.90; 1.17)	0.07 (-1.13; 1.26)	-0.23 (-1.17; 0.70)	0.21 (-1.10; 1.52)	-0.55 (-1.70; 0.61)	0.02 (-1.02; 1.06)	0.05 (-1.03; 1.13)	0.61 (-0.33; 1.56)	0.15 (-0.95; 1.24)	-0.10 (-1.14; 0.95)	Maprotiline	.	.	.	.	.	-0.14 (-0.97; 0.69)	.	.
0.23 (-0.62; 1.09)	0.16 (-0.88; 1.20)	-0.14 (-0.84; 0.56)	0.30 (-0.87; 1.47)	-0.46 (-1.45; 0.54)	0.11 (-0.72; 0.95)	0.15 (-0.75; 1.04)	0.71 (-0.06; 1.47)	0.24 (-0.67; 1.16)	-0.01 (-0.87; 0.86)	0.09 (-1.07; 1.26)	Mianserin	.	.	.	.	.	-0.09 (-0.79; 0.61)	.
0.23 (-0.54; 1.00)	0.16 (-0.81; 1.13)	-0.14 (-0.76; 0.48)	0.30 (-0.81; 1.41)	-0.46 (-1.38; 0.47)	0.11 (-0.66; 0.88)	0.14 (-0.68; 0.97)	0.71 (0.03; 1.38)	0.24 (-0.60; 1.08)	-0.01 (-0.79; 0.77)	0.09 (-1.02; 1.20)	0.00 (-0.93; 0.93)	MSZRT	.	.	.	.	.	-0.49 (-1.20; 0.22)
0.25 (-0.48; 0.98)	0.18 (-0.76; 1.11)	-0.12 (-0.69; 0.44)	0.32 (-0.77; 1.40)	-0.44 (-1.33; 0.45)	0.13 (-0.60; 0.86)	0.16 (-0.63; 0.95)	0.72 (0.09; 1.35)	0.26 (-0.55; 1.06)	0.01 (-0.73; 0.75)	0.11 (-0.97; 1.19)	0.02 (-0.88; 0.91)	0.02 (-0.81; 0.84)	Opipramol	.	.	.	.	-0.26 (-0.91; 0.38)
0.36 (-0.18; 0.90)	0.29 (-0.51; 1.09)	-0.01 (-0.30; 0.28)	0.43 (-0.54; 1.40)	-0.33 (-1.07; 0.42)	0.24 (-0.30; 0.79)	0.28 (-0.35; 0.90)	0.84 (0.43; 1.24)	0.37 (-0.27; 1.02)	0.12 (-0.44; 0.68)	0.22 (-0.75; 1.19)	0.13 (-0.63; 0.89)	0.13 (-0.54; 0.80)	0.11 (-0.51; 0.74)	Pregabalin	.	.	.	-0.52 (-0.85; -0.20)
0.30 (-0.30; 0.90)	0.23 (-0.62; 1.07)	-0.07 (-0.49; 0.35)	0.36 (-0.64; 1.36)	-0.39 (-1.18; 0.40)	0.18 (-0.44; 0.80)	0.21 (-0.47; 0.89)	0.77 (0.29; 1.25)	0.31 (-0.40; 1.01)	0.06 (-0.55; 0.67)	0.16 (-0.80; 1.12)	0.06 (-0.75; 0.88)	0.07 (-0.66; 0.79)	0.05 (-0.63; 0.73)	-0.06 (-0.54; 0.42)	Quetiapin	-0.30 (-0.91; 0.31)	.	-0.53 (-0.92; -0.13)
-0.00 (-0.62; 0.61)	-0.07 (-0.93; 0.78)	-0.37 (-0.80; 0.05)	0.06 (-0.95; 1.08)	-0.69 (-1.49; 0.11)	-0.12 (-0.75; 0.51)	-0.09 (-0.78; 0.60)	0.47 (0.03; 0.91)	0.01 (-0.71; 0.72)	-0.24 (-0.87; 0.39)	-0.14 (-0.97; 0.69)	-0.24 (-1.05; 0.58)	-0.23 (-0.97; 0.50)	-0.25 (-0.94; 0.44)	-0.36 (-0.86; 0.13)	-0.30 (-0.78; 0.18)	SSRI	.	-0.32 (-0.93; 0.30)
0.14 (-0.72; 1.00)	0.07 (-0.97; 1.11)	-0.23 (-0.93; 0.47)	0.21 (-0.97; 1.38)	-0.55 (-1.55; 0.45)	0.02 (-0.81; 0.86)	0.06 (-0.84; 0.96)	0.62 (-0.15; 1.38)	0.15 (-0.77; 1.07)	-0.10 (-0.96; 0.77)	0.00 (-1.17; 1.17)	-0.09 (-0.79; 0.61)	-0.09 (-1.02; 0.85)	-0.11 (-1.01; 0.80)	-0.22 (-0.98; 0.54)	-0.16 (-0.97; 0.66)	0.15 (-0.68; 0.97)	Tianeptine	.
-0.22 (-0.67; 0.24)	-0.29 (-1.04; 0.46)	-0.58 (-0.77; -0.40)	-0.15 (-1.07; 0.77)	-0.90 (-1.59; -0.22)	-0.33 (-0.83; 0.16)	-0.30 (-0.87; 0.26)	0.26 (-0.05; 0.57)	-0.21 (-0.80; 0.38)	-0.45 (-0.93; 0.02)	-0.35 (-1.28; 0.58)	-0.45 (-1.17; 0.27)	-0.45 (-1.06; 0.17)	-0.46 (-1.03; 0.10)	-0.58 (-0.87; -0.28)	-0.51 (-0.90; -0.13)	-0.21 (-0.63; 0.20)	-0.36 (-1.08; 0.37)	Placebo

The green cells indicate the estimates shown in Figure 3. The topright part includes estimates from direct evidence, and the bottomleft part includes estimates from mixed evidence (network estimates). The treatments of interest for the CINeMA assessment are highlighted with orange color, i.e., Benzodiazepin, placebo, Mianserin, Pregabalin, Quetiapin, Hydroxin, and Agomelatin.

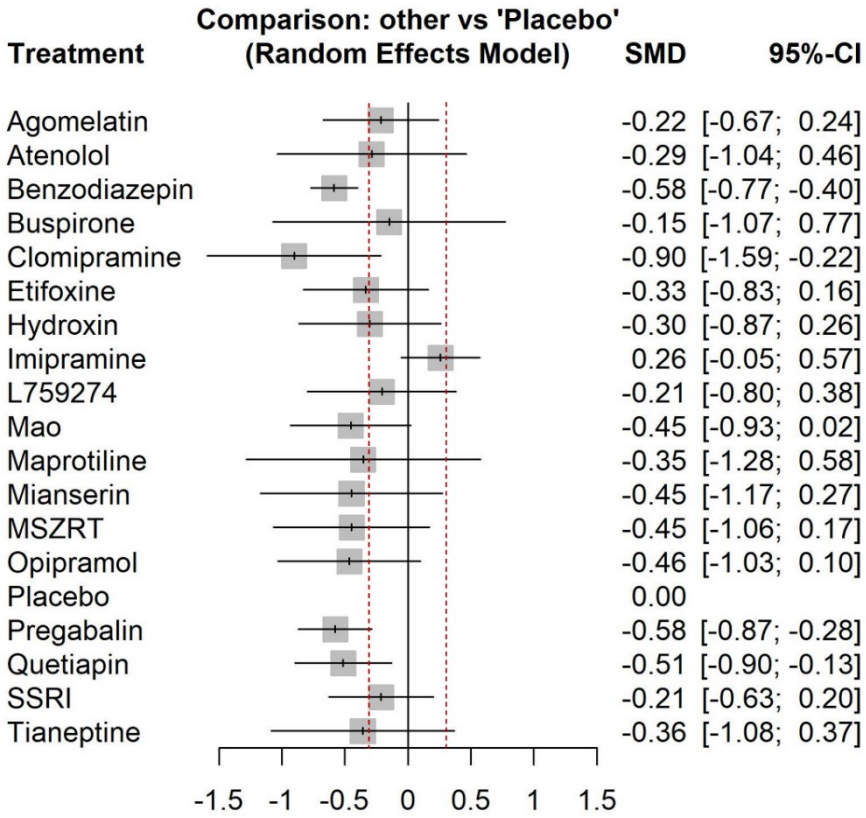


Figure 3: Forest plot for the effect of each treatment against placebo on HAMA (SMDs with 95%CIs)
Dashed lines indicate -0.3 and 0.3.

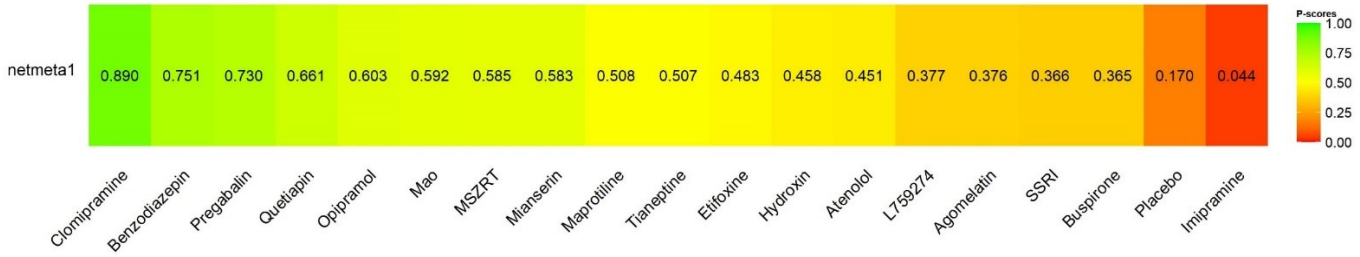


Figure 4: Ranking of treatments
Ranking of the individual treatments based on p-scores indicated with colors. P-scores describes the extent of certainty that a treatment is better than the other competing treatments.

Table 4: Results for treatment comparisons of interest (SMDs with 95%CIs)

Agomelatin	.	.	.	.	.	-0.22 (-0.67; 0.24)
0.37 (-0.12; 0.86)	Benzodiazepin	-0.19 (-0.83; 0.45)	-0.14 (-0.84; 0.56)	0.05 (-0.28; 0.37)	.	-0.60 (-0.79; -0.41)
0.09 (-0.64; 0.81)	-0.28 (-0.85; 0.28)	Hydroxin	.	.	.	-0.21 (-0.85; 0.43)
0.23 (-0.62; 1.09)	-0.14 (-0.84; 0.56)	0.15 (-0.75; 1.04)	Mianserin	.	.	.
0.36 (-0.18; 0.90)	-0.01 (-0.30; 0.28)	0.28 (-0.35; 0.90)	0.13 (-0.63; 0.89)	Pregabalin	.	-0.52 (-0.85; -0.20)
0.30 (-0.30; 0.90)	-0.07 (-0.49; 0.35)	0.21 (-0.47; 0.89)	0.06 (-0.75; 0.88)	-0.06 (-0.54; 0.42)	Quetiapin	-0.53 (-0.92; -0.13)
-0.22 (-0.67; 0.24)	-0.58 (-0.77; -0.40)	-0.30 (-0.87; 0.26)	-0.45 (-1.17; 0.27)	-0.58 (-0.87; -0.28)	-0.51 (-0.90; -0.13)	Placebo

Table 5: CINeMA assessment

Comparison	No. direct studies	Network estimate	CINeMA domains						Confidence rating
			1	2	3	4	5	6	
			Within-study bias	Reporting bias	Indirectness	Imprecision	Heterogeneity	Incoherence	
Agomelatin:Placebo	2	-0.22 (-0.67; 0.24)	Some concerns	Low risk	Major concerns	Some concerns	Some concerns	No concerns	**Very low**[1,3,4,5]
Benzodiazepin:Placebo	13	-0.58 (-0.77; -0.40)	Major concerns	Low risk	Major concerns	No concerns	Some concerns	No concerns	**Low**[1,3]
Hydroxin:Placebo	1	-0.30 (-0.87; 0.26)	Major concerns	Low risk	Major concerns	Some concerns	Some concerns	No concerns	**Very low**[1,3,4,5]
Mianserin:Placebo	0	-0.45 (-1.17; 0.27)	Major concerns	Low risk	Major concerns	Some concerns	Some concerns	No concerns	**Very low**[1,3,4,5]
Pregabalin:Placebo	4	-0.58 (-0.87; -0.28)	Major concerns	Low risk	Major concerns	No concerns	Some concerns	No concerns	**Low**[1,3]
Quetiapin:Placebo	3	-0.51 (-0.90; -0.13)	Major concerns	Low risk	Major concerns	No concerns	Some concerns	No concerns	**Low**[1,3]
Agomelatin:Benzodiazepin	0	0.37 (-0.12; 0.86)	Major concerns	Low risk	Major concerns	Some concerns	Some concerns	No concerns	**Very low**[1,3,4,5]
Agomelatin:Hydroxin	0	0.09 (-0.64; 0.81)	Major concerns	Low risk	Major concerns	Major concerns	No concerns	No concerns	**Very low**[1,3,4]
Agomelatin:Mianserin	0	0.23 (-0.62; 1.09)	Major concerns	Low risk	Major concerns	Major concerns	No concerns	No concerns	**Very low**[1,3,4]
Agomelatin:Pregabalin	0	0.36 (-0.18; 0.90)	Major concerns	Low risk	Major concerns	Some concerns	Some concerns	No concerns	**Very low**[1,3,4,5]
Agomelatin:Quetiapin	0	0.30 (-0.30; 0.90)	Major concerns	Low risk	Major concerns	Some concerns	Some concerns	No concerns	**Very low**[1,3,4,5]
Benzodiazepin:Hydroxin	1	-0.28 (-0.85; 0.28)	Major concerns	Low risk	Major concerns	Some concerns	Some concerns	No concerns	**Very low**[1,3,4,5]
Benzodiazepin:Mianserin	1	-0.14 (-0.84; 0.56)	Major concerns	Low risk	Some concerns	Major concerns	No concerns	No concerns	**Very low**[1,3,4]
Benzodiazepin:Pregabalin	4	-0.01 (-0.30; 0.28)	Major concerns	Low risk	Major concerns	No concerns	Major concerns	No concerns	**Low**[1,3]
Benzodiazepin:Quetiapin	0	-0.07 (-0.49; 0.35)	Major concerns	Low risk	Major concerns	Major concerns	No concerns	No concerns	**Very low**[1,3,4]
Hydroxin:Mianserin	0	0.15 (-0.75; 1.04)	Major concerns	Low risk	Major concerns	Major concerns	No concerns	No concerns	**Very low**[1,3,4]
Hydroxin:Pregabalin	0	0.28 (-0.35; 0.90)	Major concerns	Low risk	Major concerns	Major concerns	No concerns	No concerns	**Very low**[1,3,4]
Hydroxin:Quetiapin	0	0.21 (-0.47; 0.89)	Major concerns	Low risk	Major concerns	Major concerns	No concerns	No concerns	**Very low**[1,3,4]
Mianserin:Pregabalin	0	0.13 (-0.63; 0.89)	Major concerns	Low risk	Major concerns	Major concerns	No concerns	No concerns	**Very low**[1,3,4]
Mianserin:Quetiapin	0	0.06 (-0.75; 0.88)	Major concerns	Low risk	Major concerns	Major concerns	No concerns	No concerns	**Very low**[1,3,4]
Pregabalin:Quetiapin	0	-0.06 (-0.54; 0.42)	Major concerns	Low risk	Major concerns	Major concerns	No concerns	No concerns	**Very low**[1,3,4]

Within-study bias was evaluated based on average RoB for each comparison. Reporting bias was evaluated based on inspection of funnel plots from direct comparisions when 10 or more trials were available. Indirectness was evaluated based on on average indirectness for each comparison. Imprecision, heterogeneity, and incoherence were evaluated considering a

clinically important size of effect of 0.3 SMD. 1: Within-study bias, 2: Reporting bias, 3: Indirectness (due to differences between the population of interest and those studied.), 4: Imprecision, 5: Heterogeneity, 6: Incoherence.

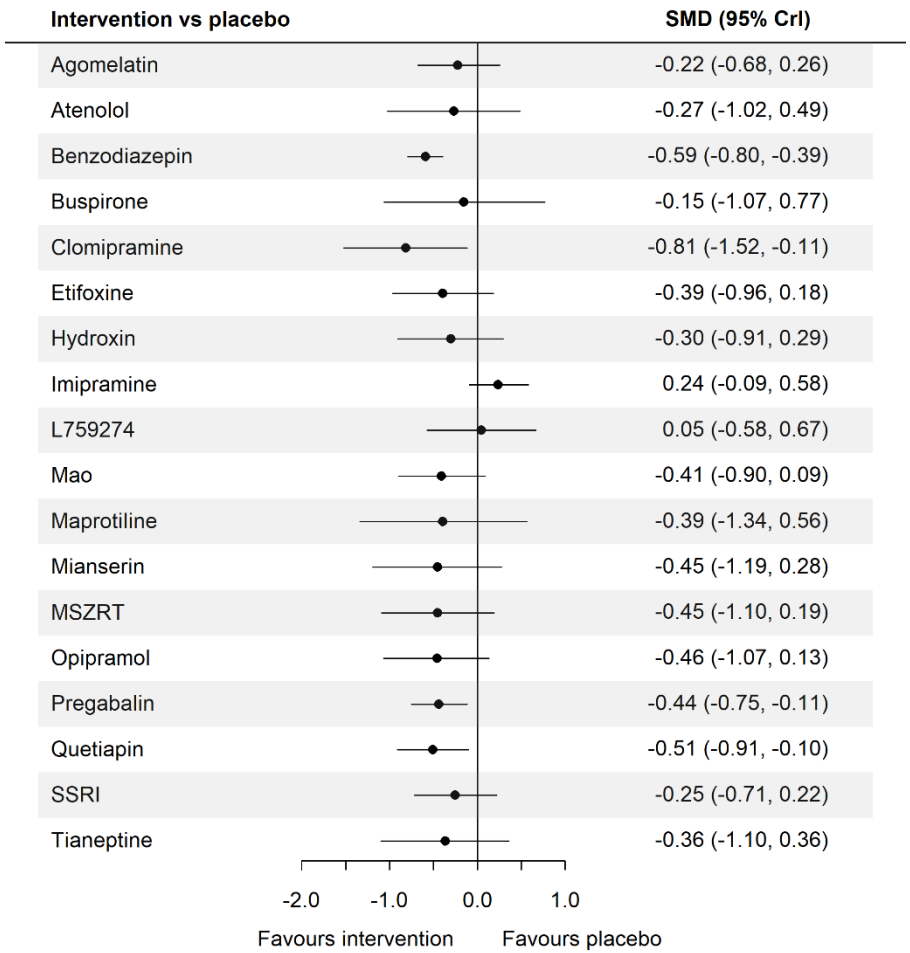


Figure 5: Forest plot for the effect of each treatment against placebo on HAMA (SMDs with 95% CrI) – Bayesian (sensitivity)

CrI=credible interval

Table 6: SUCRA (based on SMD) – Bayesian (sensitivity)

Treatment	SUCRA
Clomipramine	0.858
Benzodiazepin	0.778
Quetiapin	0.674
Opipramol	0.615
MSZRT	0.606
Mianserin	0.604
Pregabalin	0.603
Mao	0.569
Etifoxine	0.555
Maprotiline	0.548
Tianeptine	0.528
Hydroxin	0.473
Atenolol	0.449
SSRI	0.418
Agomelatin	0.396
Buspirone	0.377
L759274	0.205
Placebo	0.184
Imipramine	0.061

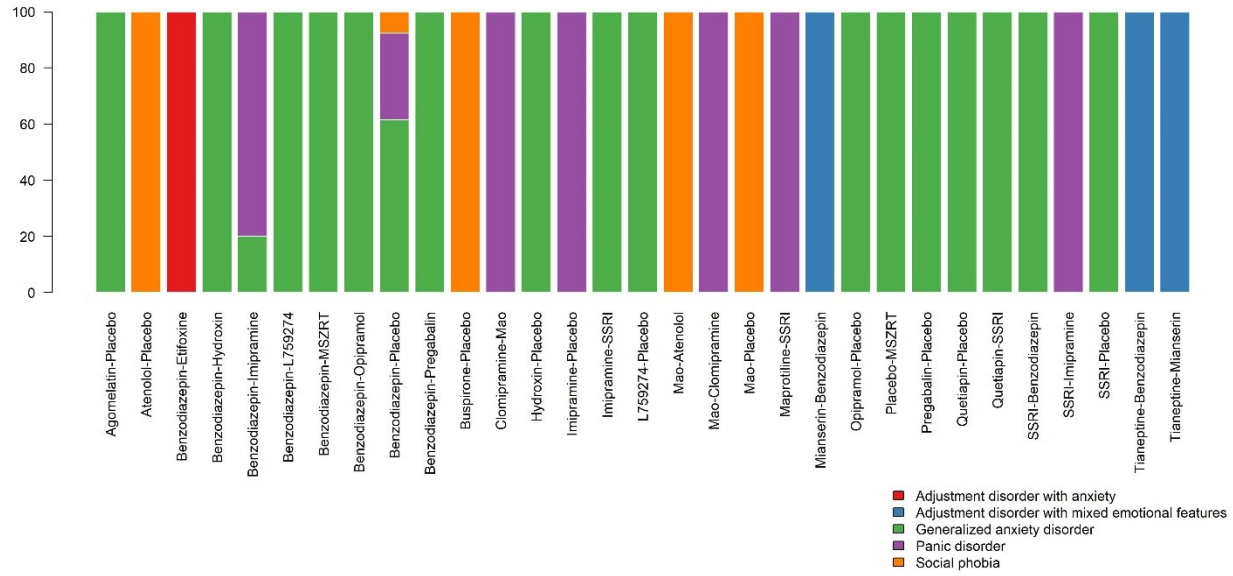
The surface under the cumulative ranking curve (SUCRA) is a numeric presentation of the overall ranking and presents a single number associated with each treatment. SUCRA values range from 0 to 1. The higher the SUCRA value, the higher the likelihood that a therapy is in the top rank or one of the top ranks; the closer to 0, the more likely that a therapy is in the bottom rank, or one of the bottom ranks.

VALIDITY OF THE NETWORK META-ANALYSES

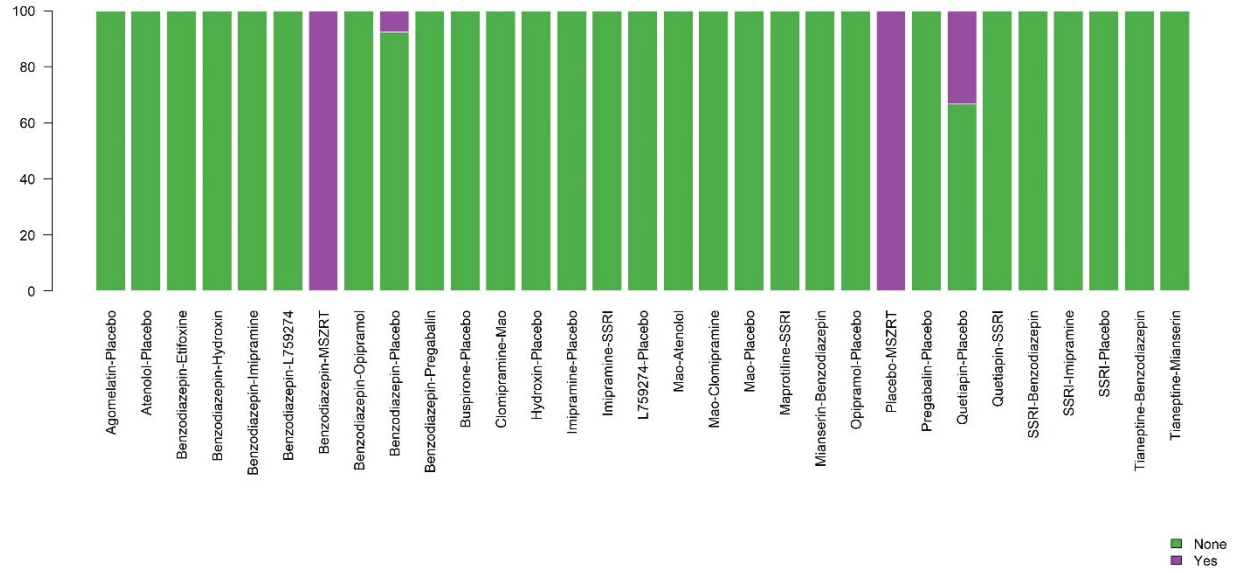
Transitivity

The transitivity assumption underlying the network meta-analyses (i.e., that the network includes studies that are sufficiently similar in important clinical and methodological characteristics).

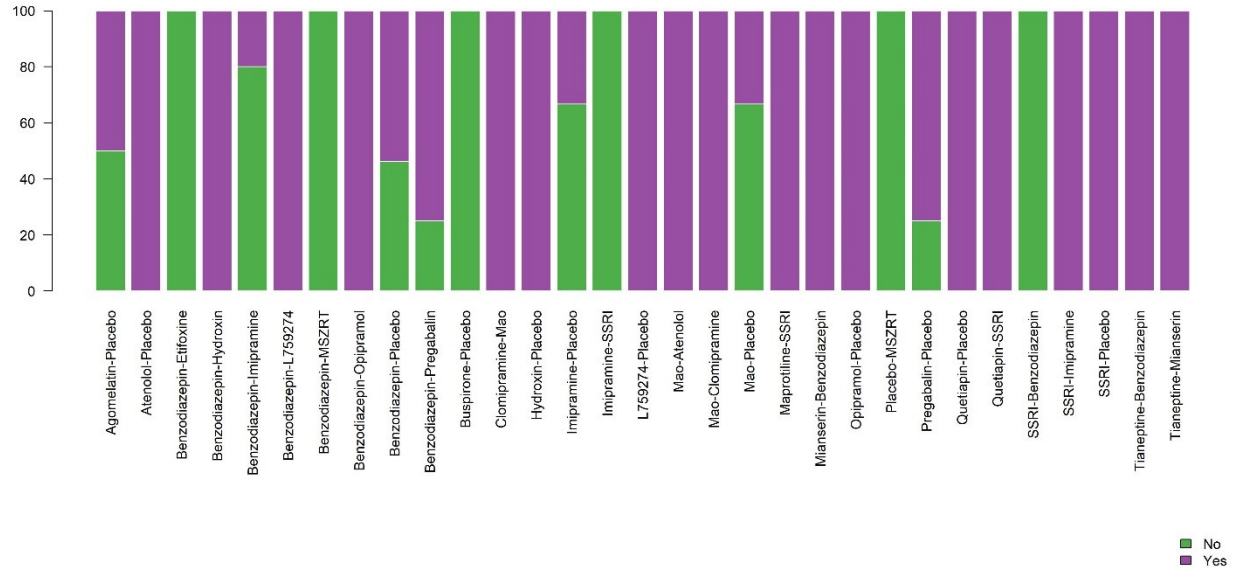
Diagnosis



Co-medication

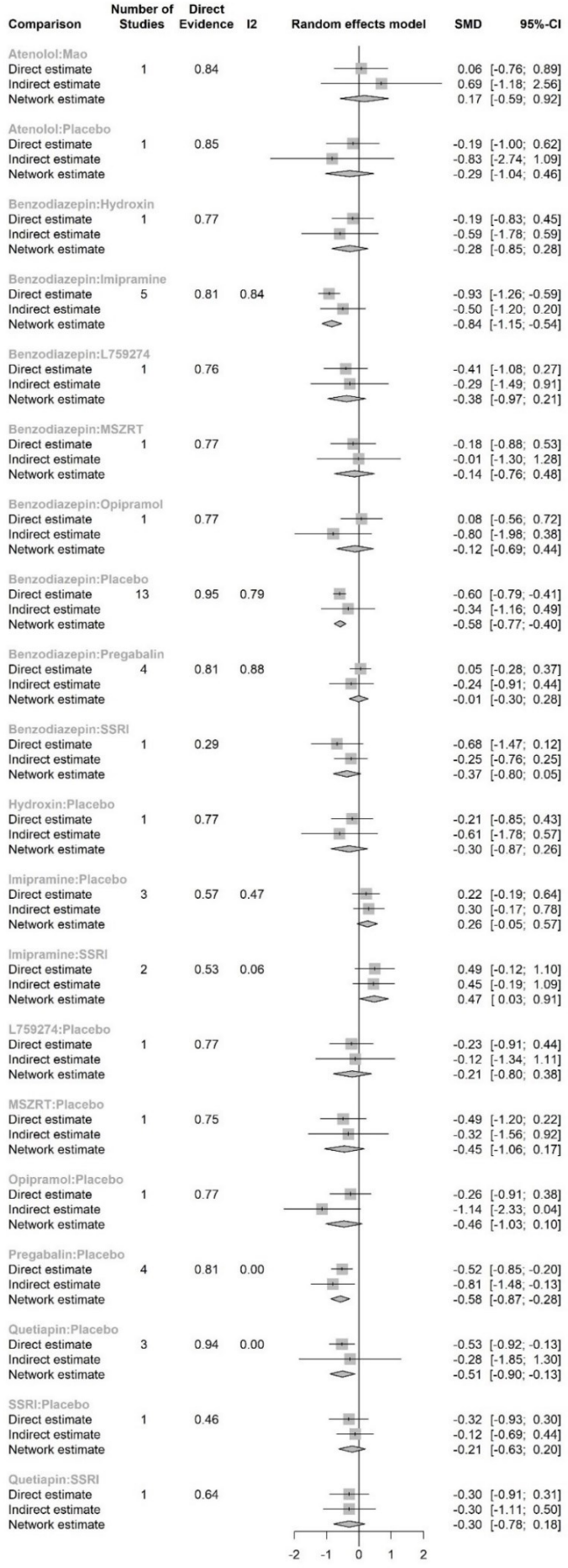


Placebo run-in



Consistency

There was no evidence of inconsistency (i.e., the agreement between direct and indirect evidence), when considering direct and indirect evidence separately with node-splitting. Below are the results for the effects of different comparisons when using only direct, only indirect and all available evidence (ideally these should not differ substantially).



DATASET

Author	ID	Duration_WD	Duration_categorical	Treatment	MD_HAMA	SD_HAMA	n_HAMA	Diagnosis	Co-medication_randomised	Placebo_run_in	RoB	Indirectness	Reporting_bias
Albus	1	8	Short	Benzodiazepin	-5.89	5.02	319	Panic disorder	None	No	3	3	2
Albus	1	8	Short	Imipramine	-1.95	5.02	273	Panic disorder	None	No	3	3	2
Albus	1	8	Short	Placebo	-1.95	5.02	220	Panic disorder	None	No	3	3	2
Amore	2	24	Short	SSRI	-9.20	5.28	14	Panic disorder	None	Yes	3	3	2
Amore	2	24	Short	Imipramine	-5.10	5.08	13	Panic disorder	None	Yes	3	3	2
Ansseau	3	6	Short	Tianeptine	-1.98	10.29	49	Adjustment disorder with mixed emotional features	None	Yes	3	2	2
Ansseau	3	6	Short	Mianserin	-2.91	10.29	52	Adjustment disorder with mixed emotional features	None	Yes	3	2	2
Ansseau	3	6	Short	Benzodiazepin	-4.32	10.29	51	Adjustment disorder with mixed emotional features	None	Yes	3	2	2
Bakish	4	8	Short	Clomipramine	-7.68	5.02	45	Panic disorder	None	Yes	3	3	2
Bakish	4	8	Short	Mao	-2.94	5.02	43	Panic disorder	None	Yes	3	3	2
Den Boer	5	6	Short	Maprotiline	-0.58	6.61	24	Panic disorder	None	Yes	3	3	2
Den Boer	5	6	Short	SSRI	0.36	6.61	20	Panic disorder	None	Yes	3	3	2
EMEA 205 - study 25	6	4	Long	Benzodiazepin	-7.63	3.28	64	Generalized anxiety disorder	None	No	3	3	2
EMEA 205 - study 25	6	4	Long	Pregabalin	-9.22	4.63	135	Generalized anxiety disorder	None	No	3	3	2
EMEA 205 - study 25	6	4	Long	Placebo	-7.86	3.60	67	Generalized anxiety disorder	None	No	3	3	2
Feltner	7	4	Short	Benzodiazepin	-8.90	6.09	64	Generalized anxiety disorder	None	Yes	3	3	2
Feltner	7	4	Short	Pregabalin	-9.26	6.21	130	Generalized anxiety disorder	None	Yes	3	3	2
Feltner	7	4	Short	Placebo	-6.07	6.09	66	Generalized anxiety disorder	None	Yes	3	3	2
Khan_a	8	8	Short	Quetiapin	-6.45	4.60	204	Generalized anxiety disorder	Yes	Yes	3	3	2
Khan_a	8	8	Short	Placebo	-4.47	4.60	198	Generalized anxiety disorder	Yes	Yes	3	3	2
Kruger	9	8	Long	Mao	-4.30	9.89	67	Panic disorder	None	Yes	3	3	2
Kruger	9	8	Long	Clomipramine	-4.60	9.89	68	Panic disorder	None	Yes	3	3	2
Lepola	10	9	Long	Benzodiazepin	-12.40	8.01	27	Panic disorder	None	No	3	3	2
Lepola	10	9	Long	Imipramine	-11.60	8.01	24	Panic disorder	None	No	3	3	2
Li	11	8	Short	Quetiapin	-9.13	5.02	11	Generalized anxiety disorder	None	Yes	3	3	2
Li	11	8	Short	Placebo	-6.40	5.02	12	Generalized anxiety disorder	None	Yes	3	3	2
Liebowitz	12	8	Long	Mao	-2.10	5.70	24	Social phobia	None	Yes	3	3	2
Liebowitz	12	8	Long	Atenolol	-1.73	5.70	22	Social phobia	None	Yes	3	3	2
Liebowitz	12	8	Long	Placebo	-0.65	5.70	26	Social phobia	None	Yes	3	3	2
Llorca	13	12	Long	Benzodiazepin	-7.08	5.02	114	Generalized anxiety disorder	None	Yes	3	3	2
Llorca	13	12	Long	Hydroxin	-6.11	5.02	102	Generalized anxiety disorder	None	Yes	3	3	2
Llorca	13	12	Long	Placebo	-5.05	5.02	108	Generalized anxiety disorder	None	Yes	3	3	2
Meridith	15	8	Short	Quetiapin	-9.6903	5.6268	413	Generalized anxiety disorder	None	Yes	3	3	2
Meridith	15	8	Short	SSRI	-8.02	5.51	203	Generalized anxiety disorder	None	Yes	3	3	2
Meridith	15	8	Short	Placebo	-6.25	5.56	212	Generalized anxiety disorder	None	Yes	3	3	2
Michelson	16	6	Short	Benzodiazepin	-7.34	4.65	62	Generalized anxiety disorder	None	Yes	3	3	2
Michelson	16	6	Short	L759274	-5.34	5.69	70	Generalized anxiety disorder	None	Yes	3	3	2
Michelson	16	6	Short	Placebo	-4.19	4.26	67	Generalized anxiety disorder	None	Yes	3	3	2
Møller	17	4	Short	Benzodiazepin	-9.17	7.52	102	Generalized anxiety disorder	None	Yes	3	3	2
Møller	17	4	Short	Opipramol	-9.77	7.52	100	Generalized anxiety disorder	None	Yes	3	3	2
Møller	17	4	Short	Placebo	-7.79	7.52	105	Generalized anxiety disorder	None	Yes	3	3	2
Nguyen	18	4	Short	Benzodiazepin	-7.60	5.45	94	Adjustment disorder with anxiety	None	No	1	1	2
Nguyen	18	4	Short	Etifoxine	-7.70	5.45	91	Adjustment disorder with anxiety	None	No	1	1	2
Noyes	19	8	Long	Benzodiazepin	-11.5075	8.383	159	Panic disorder	None	No	3	3	2
Noyes	19	8	Long	Placebo	-5.80	8.40	79	Panic disorder	None	No	3	3	2
Pande	20	4	Short	Benzodiazepin	-9.27	5.09	68	Generalized anxiety disorder	None	Yes	3	3	2
Pande	20	4	Short	Pregabalin	-6.33	5.30	139	Generalized anxiety disorder	None	Yes	3	3	2
Pande	20	4	Short	Placebo	-3.37	5.09	69	Generalized anxiety disorder	None	Yes	3	3	2
Rickels	21	4	Short	Benzodiazepin	-7.20	5.43	82	Generalized anxiety disorder	None	Yes	3	3	2
Rickels	21	4	Short	Pregabalin	-8.7683	5.4822	252	Generalized anxiety disorder	None	Yes	3	3	2
Rickels	21	4	Short	Placebo	-5.11	5.40	81	Generalized anxiety disorder	None	Yes	3	3	2
Rocca	22	8	Short	Imipramine	-5.20	3.41	26	Generalized anxiety disorder	None	No	3	3	2
Rocca	22	8	Short	SSRI	-6.20	3.41	30	Generalized anxiety disorder	None	No	3	3	2
Rocca	22	8	Short	Benzodiazepin	-8.50	3.41	25	Generalized anxiety disorder	None	No	3	3	2
Schweizer	23	8	Long	Benzodiazepin	-6.80	7.74	37	Panic disorder	None	Yes	2	3	2
Schweizer	23	8	Long	Imipramine	0.10	7.74	30	Panic disorder	None	Yes	2	3	2
Schweizer	23	8	Long	Placebo	-3.30	7.74	32	Panic disorder	None	Yes	2	3	2
Song	24	4	Short	Benzodiazepin	-5.28	5.02	49	Generalized anxiety disorder	Yes	No	3	3	2
Song	24	4	Short	Placebo	-1.94	5.02	43	Generalized anxiety disorder	Yes	No	3	3	2
Song	24	4	Short	MSZRT	-4.39	5.02	50	Generalized anxiety disorder	Yes	No	3	3	2
Stein_a	25	12	Short	Agomelatin	-5.54	8.84	63	Generalized anxiety disorder	None	Yes	2	3	2
Stein_a	25	12	Short	Placebo	-5.77	8.84	58	Generalized anxiety disorder	None	Yes	2	3	2
Stein_b	26	4	Short	Benzodiazepin	-18.11	6.32	95	Adjustment disorder with anxiety	None	No	2	1	2
Stein_b	26	4	Short	Etifoxine	-14.81	6.32	95	Adjustment disorder with anxiety	None	No	2	1	2
Stein_c	27	12	Short	Agomelatin	-5.3601	4.8871	268	Generalized anxiety disorder	None	No	2	3	2
Stein_c	27	12	Short	Placebo	-3.34	4.87	140	Generalized anxiety disorder	None	No	2	3	2

Taylor	28	8	Short	Benzodiazepin	-12.30	5.02	24	Panic disorder	None	No	3	3	2
Taylor	28	8	Short	Imipramine	-0.50	5.02	20	Panic disorder	None	No	3	3	2
Taylor	28	8	Short	Placebo	-2.50	5.02	20	Panic disorder	None	No	3	3	2
van Vliet_a	29	12	Short	Mao	1.05	4.05	15	Social phobia	None	No	2	3	2
van Vliet_a	29	12	Short	Placebo	0.02	4.05	14	Social phobia	None	No	2	3	2
van Vliet_b	30	12	Short	Buspirone	-0.95	6.19	15	Social phobia	None	No	2	3	2
van Vliet_b	30	12	Short	Placebo	-0.03	6.19	15	Social phobia	None	No	2	3	2
Versiani_a	31	12	Long	Benzodiazepin	-6.10	5.70	30	Social phobia	None	No	2	3	2
Versiani_a	31	12	Long	Placebo	-2.00	5.70	30	Social phobia	None	No	2	3	2
Versiani_b	32	8	Long	Mao	-12.60	7.76	52	Social phobia	None	No	2	3	2
Versiani_b	32	8	Long	Placebo	-4.10	7.38	26	Social phobia	None	No	2	3	2