Supplementary File 5: Summary of findings regarding response (nonpharmacologic interventions compared to second-generation antidepressants for the treatment of adult major depressive disorder).

Quality assessment							№ of patients		Effect		Strength of evidence	Notes
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Intervention	Control	Relative (95% CI)	Absolute (95% CI)		
CBT compared to SGA for MDD[1]												
5	randomized trials	not serious	not serious	not serious	serious [1]	none	142/312 (45.5%)	154/348 (44.3%)	**RR 1.10** (0.93 to 1.30)	**44 more per 1.000** (from 31 fewer to 133 more)	⊕⊕⊕◯ MODERATE	1. Few events
Acupuncture compared to SGA for MDD[1]												
93 [1]	randomized trials	not serious	not serious	serious [2]	serious [3]	none	46/73 (63.0%)	65/100 (65.0%)	**RR 1.33** (0.77 to 2.33)	**215 more per 1.000** (from 150 fewer to 865 more)	⊕⊕◯◯ LOW	1. Based on network meta-analysis; 2 studies provided direct comparisons 2. Results are based on network meta-analysis 3. Few events not meeting optimal information size
Chinese herbal medicine compared to SGA for MDD[2]												
5	randomized trials	serious [1]	not serious	not serious	serious [2]	none	594/707 (84.0%)	558/653 (85.5%)	**RR 0.99** (0.88 to 1.10)	**9 fewer per 1.000** (from 85 more to 103 fewer)	⊕⊕◯◯ LOW	1. 4 out of 5 studies are rated high risk of bias 2. Few events; study does not meet optimal information size

Quality assessment							№ of patients		Effect		Strength of evidence	Notes
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Intervention	Control	Relative (95% CI)	Absolute (95% CI)		
Exercise compared to SGA for MDD[1]												
90 [1]	randomized trials	not serious	not serious	serious [2]	serious [3]	none	31/100 (31.0%)[4]	53/100 (53.0%)[4]	**RR 0.54** (0.23 to 1.23)	**244 fewer per 1,000** (from 122 more to 408 fewer)	⨁⨁◯◯ LOW	1. Based on network meta-analysis; No studies provided data for a direct comparison 2. Estimates are based on network meta-analysis. 3. Few events, confidence intervals cross threshold of appreciable difference. 4. No data from head-head studies available. Event rate is based on average events in placebo controlled trials
Integrative therapies compared to SGA for MDD[1]												
1	randomized trials	serious [1]	not serious	not serious	serious [2]	none	98/160 (61.3%)	99/158 (62.7%)	**RR 0.98** (0.82 to 1.16)	**13 fewer per 1.000** (from 100 more to 113 fewer)	⨁⨁◯◯ LOW	1. High risk of bias due to insufficient reporting of methods and baseline differences between groups in duration of illness. 2. Sample size that does not fulfill optimal information size
Omega-3 fatty acids compared to SGA for MDD[1]												
92 [1]	randomized trials	serious [2]	not serious	serious [3]	not serious	none	9/20 (45.0%)	8/20 (40.0%)	**RR 0.51** (0.33 to 0.79)	**196 fewer per 1.000** (from 84 fewer to 268 fewer)	⨁⨁◯◯ LOW	1. Based on network meta-analysis; 2 studies provided direct comparisons 2. Suspected outcome reporting bias, only one of two studies reported response rates 3. Results are based on network meta-analysis

Quality assessment							№ of patients		Effect		Strength of evidence	Notes
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Intervention	Control	Relative (95% CI)	Absolute (95% CI)		
Saffron compared to SGA for MDD[2]												
1	randomized trials	not serious	not serious	not serious	very serious [1]	none	15/19 (78.9%)	17/19 (89.5%)	**RR 0.88** (0.67 to 1.16)	**107 fewer per 1.000** (from 143 more to 295 fewer)	⊕⊕◯◯ LOW	1. Few events; study does not meet optimal information size
SAMe compared to SGA for MDD[1]												
90 [1]	randomized trials	not serious	not serious	serious [2]	serious [3]	none	36/100 (36.0%)[4]	53/100 (53.0%)[4]	**RR 0.82** (0.44 to 1.52)	**95 fewer per 1.000** (from 276 more to 297 fewer)	⊕⊕◯◯ LOW	1. Based on network meta-analysis; 0 studies provided direct comparisons 2. Results are based on network meta-analysis 3. Small study size 4. No data from head-head trials available. Event rate is based on average events in placebo controlled trials
St. John's wort compared to SGA for MDD[1]												
9	randomized trials	not serious	serious [1]	serious [2]	not serious	none	419/770 (54.4%)	386/747 (51.7%)	**RR 1.04** (0.91 to 1.20)	**21 more per 1.000** (from 47 fewer to 103 more)	⊕⊕◯◯ LOW	1. Moderate heterogeneity (I2=47%) 2. Most studies compared to low or moderate dose SGA
Gan Mai Da Zao compared to SGA for MDD[3]												
3	randomized trials	serious [1]	not serious	not serious	very serious [2]	none	56/76 (73.7%)	52/72 (72.2%)	**RR 1.02** (0.85 to 1.22)	**14 more per 1.000** (from 108 fewer to 159 more)	⊕◯◯◯ VERY LOW	1. No blinding of study participants and personnel 2. Studies do not meet optimal information size

Quality assessment							№ of patients		Effect		Strength of evidence	Notes
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Intervention	Control	Relative (95% CI)	Absolute (95% CI)		
Third Wave CBT compared to SGA for MDD[1]												
2	randomized trial	very serious [1]	not serious	not serious	serious [2]	none	66/93 (71.0%)	76/150 (50.7%)	**RR 1.30** (1.03 to 1.56)	**152 more per 1.000** (from 15 more to 284 more)	⊕◯◯◯ VERY LOW	1. Dosage for one study capped below the upper limit of the typically prescribed range; suspected bias from one study's extremely high reported rates of response 2. Sample size does not fulfill optimal information size

CBT: Cognitive behavioral therapy; **CI:** Confidence interval; **MDD:** Major depressive disorder; **RR:** Risk ratio; **SGA:** Second generation antidepressant

Supplementary File 5. Summary of findings regarding reduction in depression score (SMD) (nonpharmacologic and pharmacologic interventions compared to inactive interventions for the treatment of adult major depressive disorder).

Quality assessment							№ of patients		Effect		Strength of evidence	Notes
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Intervention	Control	Relative (95% CI)	Absolute (95% CI)		
SGAs compared to inactive intervention for MDD[1]												
62	randomized trials	not serious	not serious	not serious	not serious	none	8555	5204	-	SMD **0.35 SD lower** (0.31 lower to 0.38 lower)	⊕⊕⊕⊕ HIGH	
Agomelatonin compared to inactive intervention for MDD[4]												
12	randomized trials	not serious	serious [1]	not serious	not serious	none	2248	1607	-	SMD **0.24 SD lower** (0.35 lower to 0.12 lower)	⊕⊕⊕◯ MODERATE	1. Some inconsistency, particularly between published and unpublished results; I-squared 66%
CBT compared to inactive intervention for MDD[5]												
5	randomized trials	not serious	not serious	not serious	serious [1]	none	509 (N total)		-	SMD **0.22 SD lower** (0.42 lower to 0.02 lower)	⊕⊕⊕◯ MODERATE	1. Optimal information size not met
St. John's wort compared to inactive intervention for MDD[6]												
16	randomized trials	not serious	serious [1]	not serious	not serious	none	2888 (N total)		-	SMD **0.49 SD lower** (0.74 lower to 0.23 lower)	⊕⊕⊕◯ MODERATE	1. I-squared 88.8%
TCA compared to inactive intervention for MDD[7]												
21	randomized trials	not serious	not serious	not serious	not serious	publication bias strongly suspected [1]	1577	1517	-	SMD **0.48 SD lower** (0.56 lower to 0.4 lower)	⊕⊕⊕◯ MODERATE	1. Asymmetric funnel plot
Alprazolam compared to inactive intervention for MDD[8]												
5	randomized trials	not serious	serious [1]	not serious	serious [2]	none	305	298	-	SMD **0.41 SD lower** (0.8 lower to 0.02 lower)	⊕⊕◯◯ LOW	1. I-squared 80% 2. Optimal information size not met
Humanistic therapies compared to inactive intervention for MDD[9]												
1	randomized trials	not serious	not serious	not serious	very serious [1]	none	51	50	-	SMD **0.06 SD higher** (0.33 lower to 0.45 higher)	⊕⊕◯◯ LOW	1. Single study with 101 participants; does not meet optimal information size

Quality assessment							№ of patients		Effect		Strength of evidence	Notes
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Intervention	Control	Relative (95% CI)	Absolute (95% CI)		
Physical exercise compared to inactive intervention for MDD[10]												
11	randomized trials	serious [1]	serious [2]	not serious	not serious	none	189	179	-	SMD **0.97 SD lower** (1.4 lower to 0.54 lower)	⊕⊕◯◯ LOW	1. Most studies did not blind outcomes assessors and did not use ITT analyses 2. Some confidence intervals do not overlap; I-squared not reported
Saffron compared to inactive intervention for MDD[2]												
2	randomized trials	not serious	not serious	not serious	very serious [1]	none	40	40	-	SMD **1.6 SD lower** (2.11 lower to 1.09 lower)	⊕⊕◯◯ LOW	1. Small studies; do not reach optimal information size
Third Wave CBT compared to inactive intervention for MDD[11]												
9	randomized trials	serious [1]	serious [2]	not serious	not serious	none	170	168	-	SMD **0.97 SD lower** (1.34 lower to 0.6 lower)	⊕⊕◯◯ LOW	1. Most trials have limitations regarding methods of randomization and blinding of outcomes assessors 2. Some confidence intervals do not overlap
Acupuncture compared to inactive intervention for MDD[12]												
3	randomized trials	serious [1]	serious [2]	not serious	very serious [3]	none	86	82	-	SMD **0.09 SD lower** (0.86 lower to 0.69 higher)	⊕◯◯◯ VERY LOW	1. One of the studies did not use ITT 2. I-squared high; some confidence intervals hardly overlap 3. Does not reach optimal information size
Chinese herbal medicine compared to inactive intervention for MDD[2]												
2	randomized trials	very serious [1]	not serious	serious [2]	serious [3]	none	113	58	-	SMD **1.05 SD lower** (1.51 lower to 0.59 lower)	⊕◯◯◯ VERY LOW	1. High risk of bias in 1 out of 2 studies 2. Unclear how applicable studies are to Western populations 3. Does not fulfill optimal information size

Quality assessment							№ of patients		Effect		Strength of evidence	Notes
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Intervention	Control	Relative (95% CI)	Absolute (95% CI)		
Integrative therapy compared to inactive intervention for MDD[9]												
1	randomized trials	serious [1]	not serious	not serious	very serious [2]	none	19	14	-	SMD **0.08 SD higher** (0.59 lower to 0.75 higher)	⊕◯◯◯ VERY LOW	1. Inadequate randomization and allocation concealment 2. Very few participants; does not meet optimal information size
Omega-3 fatty acids compared to inactive intervention for MDD[13]												
6	randomized trials	serious [1]	serious [2]	not serious	serious [3]	none	182	126	-	SMD **0.32 SD lower** (0.86 lower to 0.21 higher)	⊕◯◯◯ VERY LOW	1. Some studies do not provide ITT results and strongly favor intervention; in most studies it is unclear how the taste of omega-3 fatty acids were masked 2. I-squared 77%; Some confidence intervals do not overlap 3. Confidence interval crosses clinically relevant benefits or harms
Psychodynamic therapies compared to inactive intervention for MDD[14]												
1	randomized trials	serious [1]	not serious	not serious	very serious [2]	none	10	10	-	SMD **2.02 SD lower** (3.14 lower to 0.9 lower)	⊕◯◯◯ VERY LOW	1. Small study with unclear randomization and allocation concealment 2. Very small study; does not reach optimal information size
Tai Chi and Qigong compared to inactive intervention for MDD[15]												
3	randomized trials	serious [1]	serious [2]	not serious	serious [3]	none	91	102	-	SMD **0.96 SD lower** (1.76 lower to 0.16 lower)	⊕◯◯◯ VERY LOW	1. Outcomes assessors not blinded in all trials 2. High I-squared; some confidence intervals not overlapping 3. Does not reach optimal information size

Quality assessment							№ of patients		Effect		Strength of evidence	Notes
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Intervention	Control	Relative (95% CI)	Absolute (95% CI)		
SAMe compared to inactive intervention for MDD[16]												
2	randomized trials	not serious	Serious [1]	not serious	very serious [2]	none	74	68	-	SMD 0.54 **SD lower** (1.54 lower to 0.46 higher)	⊕◯◯◯ VERY LOW	1. High I-squared 2. Does not reach optimal information size
Bright light therapy compared to inactive intervention for MDD[17]												
1	randomized trials	not serious	not serious	not serious	very serious [1]		32	30	-	SMD **0.79 SD lower** (1.31 lower to 0.28 lower)	⊕⊕◯◯ LOW	1. Does not reach optimal information size

CBT: Cognitive behavioral therapy; **CI:** Confidence interval; **MDD:** Major depressive disorder; **RR:** Risk ratio; **SAMe:** S-adenosyl methionine; **SGA:** Second generation antidepressant; **SMD:** Standardized mean difference

Supplementary File 5. Summary of findings regarding overall discontinuation (nonpharmacologic interventions compared to inactive interventions for the treatment of adult major depressive disorder).

Quality assessment							№ of patients		Effect		Strength of evidence	Notes
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Intervention	Control	Relative (95% CI)	Absolute (95% CI)		
CBT compared to inactive intervention for MDD[18]												
7	randomized trials	serious [1]	not serious	not serious	serious [2]	none	51/398 (12.8%)	60/436 (13.8%)	**RR 1.01** (0.59 to 1.72)	**1 more per 1.000** (from 56 fewer to 99 more)	⊕⊕◯◯ LOW	1. Outcomes assessors often not blinded 2. Few events; confidence intervals cross clinically relevant benefits or harms
Omega-3 fatty acids compared to inactive intervention for MDD[13]												
7	randomized trials	serious [1]	not serious	not serious	serious [2]	none	61/272 (22.4%)	45/174 (25.9%)	**RR 0.87** (0.60 to 1.26)	**34 fewer per 1.000** (from 67 more to 103 fewer)	⊕⊕◯◯ LOW	1. Some studies do not provide ITT results and strongly favor intervention; in most studies it is unclear how the taste of omega-3 fatty acids were masked 2. Confidence interval crosses clinically relevant benefits or harms
Saffron compared to inactive intervention for MDD[2]												
2	randomized trials	not serious	not serious	not serious	very serious [1]	none	2/40 (5.0%)	7/40 (17.5%)	**RR 0.29** (0.06 to 1.30)	**124 fewer per 1.000** (from 53 more to 164 fewer)	⊕⊕◯◯ LOW	1. Few events; study does not reach optimal information size
SGAs compared to inactive intervention for MDD[19]												
5	randomized trials	not serious	not serious	not serious	serious [1]	publication bias strongly suspected [2]	70/674 (10.4%)	58/521 (11.1%)	**RR 1.03** (0.69 to 1.54)	**3 more per 1.000** (from 35 fewer to 60 more)	⊕⊕◯◯ LOW	1. Few events; does not meet optimal information size 2. Not all trials report overall discontinuation
St. John's wort compared to inactive intervention for MDD[19]												
4	randomized trials	not serious	not serious	not serious	very serious [1]	none	26/334 (7.8%)	29/285 (10.2%)	**RR 0.84** (0.49 to 1.45)	**16 fewer per 1.000** (from 46 more to 52 fewer)	⊕⊕◯◯ LOW	1. Very few events; optimal information size not reached
TCA compared to inactive intervention for MDD[19]												

Quality assessment							№ of patients		Effect		Strength of evidence	Notes
№ of studies	**Study design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**Intervention**	**Control**	**Relative (95% CI)**	**Absolute (95% CI)**		
4	randomized trials	serious [1]	not serious	not serious	serious [2]	none	50/246 (20.3%)	53/238 (22.3%)	**RR 0.91** (0.46 to 1.78)	**20 fewer per 1.000** (from 120 fewer to 174 more)	⊕⊕◯◯ LOW	1. 3 out of 4 studies have serious limitations 2. Few events; does not meet optimal information size
SAMe compared to inactive intervention for MDD[16]												
2	randomized trials	not serious	not serious	not serious	very serious [1]	none	29/74 (39.2%)	31/68 (45.6%)	**RR 0.88** (0.61 to 1.29)	**55 fewer per 1.000** (from 132 more to 178 fewer)	⊕⊕◯◯ LOW	1. Very few events
Bright light therapy compared to inactive intervention for MDD[17]												
1	randomized trials	not serious	not serious	not serious	very serious [1]	none	4/32 (12.5%)	6/30 (20.0%)	**RR 0.63** (0.20 to 2.00)	**74 fewer per 1.000** (from 160 fewer to 200 more)	⊕⊕◯◯ LOW	1. Very few events

CBT: Cognitive behavioral therapy; **CI:** Confidence interval; **MDD:** Major depressive disorder; **RR:** Risk ratio; **SAMe:** S-adenosyl methionine**; SGA:** Second generation antidepressant

Supplementary File 5. Summary of findings regarding discontinuation due to adverse events (nonpharmacologic interventions compared to inactive interventions for the treatment of adult major depressive disorder).

Quality assessment							№ of patients		Effect		Strength of evidence	Notes
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Intervention	Control	Relative (95% CI)	Absolute (95% CI)		
SGAs compared to inactive intervention for MDD[19]												
6	randomized trials	not serious	not serious	not serious	serious [1]	publication bias strongly suspected [2]	41/865 (4.7%)	18/707 (2.5%)	**RR 1.88** (1.07 to 3.28)	**22 more per 1.000** (from 2 more to 58 more)	⊕⊕◯◯ LOW	1. Few events; does not meet optimal information size 2. Not all trials report discontinuation because of adverse events
St. John's wort compared to inactive intervention for MDD[19]												
3	randomized trials	not serious	not serious	not serious	very serious [1]	none	6/286 (2.1%)	6/236 (2.5%)	**RR 0.92** (0.29 to 2.94)	**2 fewer per 1.000** (from 18 fewer to 49 more)	⊕⊕◯◯ LOW	1. Very few events; optimal information size not reached
TCA compared to inactive intervention for MDD[19]												
3	randomized trials	serious [1]	not serious	not serious	serious [2]	none	15/214 (7.0%)	9/207 (4.3%)	**RR 1.64** (0.72 to 3.75)	**28 more per 1.000** (from 12 fewer to 120 more)	⊕⊕◯◯ LOW	1. 2 out of 3 studies have serious limitations 2. Few events; does not meet optimal information size
SAMe compared to inactive intervention for MDD[16]												
1	randomized trials	not serious	not serious	not serious	very serious [1]	none	3/64 (4.7%)	4/60 (6.7%)	**RR 0.70** (0.16 to 3.01)	**20 fewer per 1.000** (from 56 fewer to 134 more)	⊕⊕◯◯ LOW	1. Very few events
Bright light therapy compared to inactive intervention for MDD[17]												
1	randomized trials	not serious	not serious	not serious	very serious [1]	none	1/32 (3.1%)	1/30 (3.3%)	**RR 0.94** (0.06 to 14.33)	**2 fewer per 1.000** (from 31 fewer to 444 more)	⊕⊕◯◯ LOW	1. Very few events

CI: Confidence interval; **MDD:** Major depressive disorder; **RR:** Risk ratio; **SAMe:** S-adenosyl methionine**; SGA:** Second generation antidepressant

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