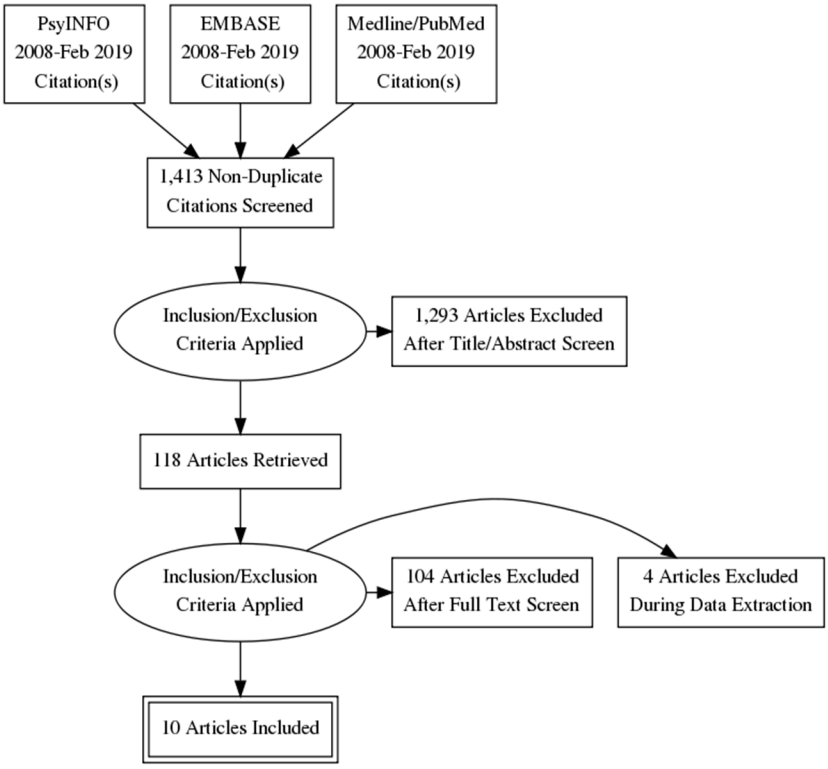
Chapter 6: Complementary and Integrative Health and other Non-Conventional Approaches for Treating Generalized Anxiety Disorder (GAD)

Results of the Literature Search for GAD

Extensive literature searches identified 1,413 citations (after duplicates removed) potentially addressing the CIH and other interventions of interest for the treatment of GAD. Of those, 1,293 were excluded upon title and abstract review for clearly not meeting inclusion criteria (e.g., not pertinent to the topic, not published in English, published prior to study inclusion publication date, or not a full-length article). A total of 118 full-length articles were retrieved for review (See Figure 1 for the PRISMA diagram). Of those, 104 were excluded due to having the wrong patient population (66 studies), the wrong study design (21 studies), the wrong intervention (11 studies), less than 20 patients (3 studies), more recent and/or comprehensive systematic review available (2 studies), and wrong outcomes (1 study). An additional 4 studies were excluded during data abstraction. Reasons for these exclusions are listed in **Appendix B**.

Figure 1. Prisma Study Flow Diagram for GAD



Overall, 10 studies were included in the systematic review for GAD. **Table 1** presents a summary of the evidence (how many RCTs and/or SRs) for each CIH and other non-conventional intervention.

Table 1. Overview of Evidence for CIH and other Non-Conventional Interventions to Treat Generalized Anxiety Disorder

Intervention	Number and Type of Studies
Accelerated Resolution Therapy (ART)	0
Acupuncture	0
Art therapy	0
Cannabinoids	0
Chiropractic care	0
Equine therapy	0
Exercise therapy (outdoor therapy)[1]	1 RCT (in 4 publications reporting on different outcomes)
Healing Touch	0
Hyperbaric Oxygen Therapy	0
Massage therapy	1 RCT
Meditation	0
Music therapy	0
Tai chi	0
Relaxation therapy	5 RCTs
Therapeutic Touch	0
Training and caring for service dogs	0
Transcranial Magnetic Stimulation (TMS)	3 RCTs
Yoga	0
Total Studies	**10 studies (all RCTs)**

RCT: Randomized controlled trial; SR: systematic review

All of the full-text studies included in this report along with further details of the search terms and concepts used to guide the searches for GAD are provided in a supplemental file on Max.gov and can be accessed here: https://community.max.gov/display/VAExternal/GAD+Report+Supplementary+Materials

[1] It is important to note that types of exercise vary across studies and conditions. Outdoor therapy was identified in the CARA legislation, while exercise was identified by the COVER Commission as an intervention of interest. These have been combined due to the overlap in the studies.

Exercise

Evidence Base

Our searches of the literature identified 1 RCT published in four publications reporting on separate outcomes for the same population of patients who received resistance or aerobic exercise as an adjunct treatment to pharmacotherapy for the treatment of Generalized Anxiety Disorder (Herring et al, 2011; Herring et al., 2012; Herring et al., 2015; Herring et al., 2016). The overall strength of the evidence for all the reported outcomes of interest was rated low to very low (**See Table 1**). This is largely due to the methodologic quality of the study and the small sample size.

Herring et al. conducted an RCT in which thirty sedentary women were randomized to receive 6 weeks of resistance exercise therapy (RET, n=10), aerobic exercise therapy (AET, n=10) or waitlist (n=10). The patients were all female and were aged 18 to 37 years. **Table 3** presents more information about the characteristics of the enrolled patients. The primary outcomes of interest in the RCT were reduction in symptoms of anxiety, pain, remission, quality of life, and sleep

The exercise interventions (RET; AET) consisted of two sessions per week for six weeks. For RET, patients engaged in seven sets of 10 repetitions each of leg curl, leg extension, and leg press exercises starting at 50% of predicted one-repetition maximum (1-RM) during week and then increased by 5% of 1-RM weekly. Each exercise began with a warm-up set of ten repetitions beginnings at 35% of 1-RM in week 1 and then increasing by 5% of 1-RM each week. The AET was matched to RET in terms of active time spent exercising, positive work completed, 5% progression in intensity each week, and body region exercised. Patients in the AET group engaged in 16 min. of continuous dynamic leg cycling exercise twice per week. Patients in the waitlist group were delayed entry to an active intervention group for 6 weeks but completed the same outcome assessments as those in the intervention groups.

Study Quality

Using the Cochrane tool, we rated the RoB of the RCT as having some concerns primarily due to no blinding of patients or clinicians. See **Table 4** for individual quality ratings.

Key Findings

Below, we describe the key findings for the outcomes of interest with the GRADE strength of the evidence (SOE) rating. See **Table 1** for factors that influenced the SOE ratings.

- Evidence from 1 RCT suggests there is no significant difference between exercise and waitlist control in improving symptoms of anxiety (SOE: Very low)
- Evidence from 1 RCT suggests that exercise statistically significantly reduces worry symptoms immediately following treatment compared to waitlist control. (SOE: Low)
- Evidence from 1 RCT found no significant difference between exercise and waitlist control in improving symptoms of depression. (SOE: Very low)
- Evidence from 1 RCT suggests there is no significant difference between exercise and waitlist control in reducing pain. (SOE: Very low)
- Evidence from 1 RCT suggests that exercise yielded statistically significant improvements in both duration of sleep [time in bed] and continuity of sleep [sleep onset latency and sleep efficiency] compared to waitlist control (Very low).
- Evidence from 1 RCT suggests that exercise statistically significantly improves both quality of life in terms of physical functioning and mental health compared to waitlist control (SOE: Low).

- Evidence from 1 RCT found no significant difference between exercise and waitlist control in improving quality of life in terms of social functioning (SOE: Low).

Discussion

Overall, the results of the Herring et al. RCT suggest that short-term exercise training improves worry symptoms, quality of life, and sleep outcomes among patients with GAD. More specifically, resistance exercise training (RET) statistically significantly reduced feelings of anxiety-tension and the frequency and intensity of irritability. While not reaching statistical significance, both RET and aerobic exercise training (AET) also resulted in improvements in trait anxiety, concentration, depressive symptoms, fatigue, vigor, and the intensity of pain with effects being larger for RET compared to AET, albeit not significantly so. See **Table 3** for more details about the results of the RCT. The overall strength of the evidence for all the reported outcomes of interest was rated low (**See Table 1**). This is largely due to limitations in the methodological quality of the study and the small sample size.

Table 1. Strength of Evidence for Exercise to Treat GAD

Outcome	Quantity and Type of Evidence	Intervention (n)/ Control (n)/Follow-up	Estimate of Effect	Study Limitations (Risk of Bias)	Inconsistency	Indirectness	Imprecision	Publication Bias	GRADE of Evidence for Outcome
Anxiety symptoms	1 RCT (Herring, 2011)	RET (n=10) vs. AET (n=10) vs. WL (n=10) 6 wks.	**Change in STAI-Trait** (mean [SD]): **Post-tx:** 44.10 (11.46); 45.30 (8.15); 52.80 (9.43); ES, 95% CI (RET; AET): 0.52, -0.37 to 1.41; 0.54, -0.36 to 1.43; **NS**	Yes (-1)	No	No	Yes (-2); small sample size; wide 95% CI	No	Very low
Worry symptoms	1 RCT (Herring, 2011; 2012)	RET (n=10) vs. AET (n=10) vs. WL (n=10) 6 wks.	**Change in CES-D** (mean [SD]): **Post-tx:** 61.10 (10.01); 59.30 (7.38); 65.50 (7.62); ES, 95% CI (RET; AET): 0.45, -0.45 to 1.33; 0.45, -0.44 to 1.34; **favors exercise**	Yes (-1)	No	No	Yes (-1); small sample size	No	Low
Depression symptoms	1 RCT (Herring, 2011)	RET (n=10) vs. AET (n=10) vs. WL (n=10) 6 wks.	**Change in BDI-II** (mean [SD]): **Post-tx:** BDI-II: 8.10 (7.59); 10.10 (12.11); 16.90	Yes (-1)	No	No	Yes (-2); small sample size; wide 95% CI	No	Very low

Outcome	Quantity and Type of Evidence	Intervention (n)/ Control (n)/Follow-up	Estimate of Effect	Study Limitations (Risk of Bias)	Inconsistency	Indirectness	Imprecision	Publication Bias	GRADE of Evidence for Outcome
			(10.87); ES, 95% CI (RET; AET): 0.52, -0.37 to 1.41; 0.04, -0.84 to 0.91; **NS**						
Pain	1 RCT (Herring, 2016)	RET (n=10) vs. AET (n=10) vs. WL (n=10) 6 wks.	Pain, no locations (# painful locations pain figure drawing): 2.60 (3.06); 2.30 (2.95); 1.50 (3.44); ES, 95% CI (RET; AET): -0.64, -1.54 to 0.26; -0.04, -0.91 to 0.84; **NS** Pain, VAS (visual analog scale for pain): 12.30 (12.33); 20.30 (24.24); 7.70 (12.76); ES, 95% CI (RET; AET): 0.43, -0.45 to 1.32; -0.13, -1.01 to 0.75); **NS**	Yes (-1)	No	No	Yes (-2); small sample size; wide 95% CI	No	Very low

Outcome	Quantity and Type of Evidence	Intervention (n)/ Control (n)/Follow-up	Estimate of Effect	Study Limitations (Risk of Bias)	Inconsistency	Indirectness	Imprecision	Publication Bias	GRADE of Evidence for Outcome
Sleep	1 RCT (Herring, 2015)	RET (n=10) vs. AET (n=10) vs. WL (n=10) 6 wks.	TST: 466 (62); 475 (81); 546 (168); ES, 95% CI (RET; AET): -0.90, -1.87 to 0.07; -0.72, -1.70 to 0.26; **NS** Lights out Time (military time): 00.40 (65); 01.37 (106); 23.31 (161); ES, 95% CI (RET; AET): 0.63, -0.32 to 1.57; 0.31; -0.65 to 1.27; **NS** Awakening out of bed (military time): 08.47 (105); 10.07 (107); 10.27 (180); ES, 95% CI (RET; AET): -0.92, -1.89 to 0.05; -0.85, -1.84 to 0.15; **NS** TIB (min.): 493 (59); 517 (83);	Yes (-1)	No	No	Yes (-2); small sample size; wide 95% CI	No	Very low

Outcome	Quantity and Type of Evidence	Intervention (n)/ Control (n)/Follow-up	Estimate of Effect	Study Limitations (Risk of Bias)	Inconsistency	Indirectness	Imprecision	Publication Bias	GRADE of Evidence for Outcome
			627 (168); ES, 95% CI (RET; AET): -1.79, -2.89 to -0.70; -1.13, -2.16 to -0.11; **favors exercise** SOL (min.): 12 (9); 11 (9); 28 (39); ES, 95% CI (RET; AET): -1.30, -2.32 to -0.28; -1.08, -2.09 to -0.06; **favors exercise** WASO (min.): 6 (10); 7 (9); 18 (86); ES, 95% CI (RET; AET): -0.27, -1.20 to 0.66; -0.28, -1.23 to 0.68; **NS** Sleep efficiency (%): 93.2 (4.8); 91.7 (3.9); 86.7 (10.6); ES, 95% CI (RET; AET): 1.30, 0.29 to 2.32; 0.68, -						

Outcome	Quantity and Type of Evidence	Intervention (n)/ Control (n)/Follow-up	Estimate of Effect	Study Limitations (Risk of Bias)	Inconsistency	Indirectness	Imprecision	Publication Bias	GRADE of Evidence for Outcome
			0.30 to 1.66; **favors RET**						
Quality of life	1 RCT (Herring, 2016)	RET (n=10) vs. AET (n=10) vs. WL (n=10) 6 wks.	SF-36 (mean [SD]; ES, 95% CI): Physical functioning: 0 (8.16); 0.76, -0.14 to 1.67; 2.5 (7.2); 1.31, 0.34 to 2.27; -7.5 (10.3); **favors AET** Social functioning: 13 (13.0); -.12, -0.76 to 0.99; 10.3 (13.9); -0.01, -0.89 to 0.87; 10.5 (22.6); **NS** Mental health: 16.4 (16.7); 1.05, 0.11 to 1.98; 9.6 (7.4); 0.75, -0.16 to 1.65; -3.6 (10.7); **favors RET**	Yes (-1)	No	No	Yes (-1); small sample size	No	Low

CI: confidence interval; CT: control group; ES: effective size; f/u: follow-up; mos.: months; NR: not reported; NS: not significant; RCT: randomized controlled trials; SD: standard deviation

Table 2. GRADE Factors Used to Assess the Quality of a Body of Evidence

Evidence Category	Definition
Study Quality (Internal Validity or Risk of Bias)	Study quality considers the overall risk of bias rating of all the studies included in the evidence base. In this review, the overall risk of bias would be the average or median USPSTF rating for studies comprising an evidence base for a key outcome.
Consistency of Evidence	Consistency of evidence refers to the degree of similarity in the direction of effects or the degree of similarity in the effect sizes (magnitude of effect) across individual studies within an evidence base.
Directness of Evidence	Direct evidence directly compares interventions of interest in populations of interest and measures patient-oriented outcomes. Evidence can be indirect if the tested intervention differs from the intervention of interest, the study population differs from the population of interest, the outcomes differ from those of primary interest, or treatment comparisons have not been tested in head-to-head comparisons.
Precision of Evidence	Precision is the degree of certainty surrounding an estimate of effect with respect to an outcome. Precision is primarily assessed by examining the 95% confidence intervals around the summary effect size.

Link to GRADE Handbook: **http://gdt.guidelinedevelopment.org/app/handbook**

Table 3. Evidence Table for RCTs on Exercise to Treat GAD

Study Details	Study Population	Treatment	Results	Conclusion/Limitations
Reference: Herring et al. (2011; 2012; 2-15; 2016) **Purpose:** To quantify and compare the effects of 6 wks. of resistance and aerobic exercise on symptoms of GAD **Setting:** The University of Georgia **F/u:** 6 wks. **Funding source:** University of Georgia	**Number of patients:** 30; n=10 RET; n=10 AET; n=10 WL **Inclusion criteria:** Women aged 18-39 years; diagnosed with GAD according to DSM-IV **Exclusion criteria:** Score < 45 on Penn State Worry Questionnaire; score < 7 on GAD section on Psychiatric Diagnostic Screening Questionnaire; expending > than 250 kilocalories per kilogram body weight/wk. as measured by 7-day physical activity and recall questionnaire; engaging in > 6 exercise bouts in month prior to recruitment; pregnancy; any medical contradictions (cardiovascular, musculoskeletal) to exercise training according to American College of Sports Medicine guidelines **Pt. baseline characteristics (RET; AET; WL):** Age (mean yrs. [SD]): 25.6 (7.1); 20.7 (3.0); 24.2 (6.3) Gender (% female): 100%; 100%; 100% Medication type (n) Contraceptive: 5; 5; 5 SSRI: 2; 2; 3 SNRI: 1; 1; 0 NDRI: 0; 1; 1 Muscle relaxant: 1; 1; 0 Psychostimulant: 0; 0; 1 Antibiotic: 0; 1; 0	**Intervention:** RET consisted on lower-body strength training 2 times per week for 6 weeks at an intensity progressing from 50% to 75% predicted 1-RM AET consisted of 6 weeks of dynamic leg cycling exercise 2 times per week and matched to the strength training arm on total positive work completed, total time actively engaged in exercise and weekly load progression **Control:** WL in which patients maintained current lifestyle and did not enter the 6-week exercise training intervention, but completed the same outcome measures as those in the active interventions **Outcomes of Interest:** Worry symptoms measured using the Penn State Worry Questionnaire (PSWQ); trait anxiety symptoms measured using the State-Trait Anxiety Inventory (STAI-Trait), Profile of Mood States Brief Form (POMS-B), and Irritability Questionnaire (IRQ); depression measured with BDI-II; remission rates; total sleep time (TST); lights out time; awakening out of bed time; time in bed (TIB); sleep onset latency (SOL); wakefulness after sleep onset (WASO); sleep efficiency; QoL measured with SF-36	**<u>Post-Intervention</u>** **Anxiety symptoms (RET; AET; WL):** STAI-Trait (Mean [SD]): 44.10 (11.46); 45.30 (8.15); 52.80 (9.43) ES, 95% CI (RET; AET): 0.52, -0.37 to 1.41; 0.54, -0.36 to 1.43; NS POMS-T (anxiety-tension): 2.80 (2.66); 4.50 (4.43); 7.00 (4.16); ES, 95% CI (RET; AET): 1.05, 0.12 to 1.99; 0.73, -0.18 to 1.63; favors RET POMS-C (confusion): 3.10 (1.79); 3.10 (2.42); 5.70 (2.21); ES, 95% CI (RET; AET): 0.54, -0.35 to 1.43; 0.34, -0.54 to 1.23; NS POMS-F (fatigue): 4.90 (3.90); 4.70 (4.83); 6.50 (4.93); ES, 95% CI (RET; AET): 0.39, -0.49 to 1.28; 0.37, -0.51 to 1.26; NS POMS-V (vigor): 7.30 (4.47); 7.20	**Conclusion:** Results suggest that RET significantly reduced feelings of anxiety-tension and the frequency and intensity of irritability when compared to AET and WL. Exercise led to greater remission and greater improvement in worry symptoms compared to WL. Both types of exercise statistically significantly reduced time in bed and sleep onset latency and RET led to increased sleep efficiency. In terms of QoL, AET resulted in statistically significant improvements in physical functioning, while RET resulted in statistically significant improvements in mental health. **Limitations:** Small sample size **Study ROB:** Some concerns; due primarily to no blinding of patients, clinicians, lack of ITT analysis. **Author conflict:** None reported

Study Details	Study Population	Treatment	Results	Conclusion/Limitations
	Antihistamine: 1; 0; 0		(3.68); 4.10 (3.70); ES, 95% CI (RET; AET): 0.65, -0.25 to 1.55; 0.59, -0.30 to 1.49; NS **Worry symptoms (RET; AET; WL):** PSWQ: 61.10 (10.01); 59.30 (7.38); 65.50 (7.62); ES, 95% CI (RET; AET): 0.45, -0.45 to 1.33; 0.45, -0.44 to 1.34; favors exercise **Depression symptoms (RET; AET; WL):** BDI-II: 8.10 (7.59); 10.10 (12.11); 16.90 (10.87); ES, 95% CI (RET; AET): 0.52, -0.37 to 1.41; 0.04, -0.84 to 0.91; NS **Irritability (RET; AET; WL):** IRQ-F (frequency): 19.80 (8.66); 19.10 (9.59); 32.40 (7.38); ES, 95% CI (RET; AET): 1.18, 0.33 to 2.03; 0.88, -0.04 to 1.80; favors RET IRQ-I (intensity): 19.90 (9.96); 19.50 (7.72); 34.10 (6.95); ES, 95% CI (RET;	

Study Details	Study Population	Treatment	Results	Conclusion/Limitations
			AET): 1.23, 0.28 to 2.19; 0.74, -0.17 to 1.64; favors RET **Pain (RET; AET; WL):** Pain, no locations (# painful locations pain figure drawing): 2.60 (3.06); 2.30 (2.95); 1.50 (3.44); ES, 95% CI (RET; AET): -0.64, -1.54 to 0.26; -0.04, -0.91 to 0.84; NS Pain, VAS (visual analog scale for pain): 12.30 (12.33); 20.30 (24.24); 7.70 (12.76); ES, 95% CI (RET; AET): 0.43, -0.45 to 1.32; -0.13, -1.01 to 0.75); NS **Sleep (RET; AET; WL [min.])** TST: 466 (62); 475 (81); 546 (168); ES, 95% CI (RET; AET): -0.90, -1.87 to 0.07; -0.72, -1.70 to 0.26; NS Lights out Time (military time): 00.40 (65); 01.37 (106); 23.31 (161); ES, 95% CI (RET; AET): 0.63,	

Study Details	Study Population	Treatment	Results	Conclusion/Limitations
			-0.32 to 1.57; 0.31; -0.65 to 1.27; NS Awakening out of bed (military time): 08.47 (105); 10.07 (107); 10.27 (180); ES, 95% CI (RET; AET): -0.92, -1.89 to 0.05; -0.85, -1.84 to 0.15; NS TIB (min.): 493 (59); 517 (83); 627 (168); ES, 95% CI (RET; AET): -1.79, -2.89 to -0.70; -1.13, -2.16 to -0.11; favors exercise SOL (min.): 12 (9); 11 (9); 28 (39); ES, 95% CI (RET; AET): -1.30, -2.32 to -0.28; -1.08, -2.09 to -0.06; favors exercise WASO (min.): 6 (10); 7 (9); 18 (86); ES, 95% CI (RET; AET): -0.27, -1.20 to 0.66; -0.28, -1.23 to 0.68; NS Sleep efficiency (%): 93.2 (4.8); 91.7 (3.9); 86.7 (10.6); ES, 95% CI (RET; AET): 1.30, 0.29 to 2.32; 0.68, -0.30 to 1.66; favors RET **QoL pre/post change (mean [SD]; ES,**	

Study Details	Study Population	Treatment	Results	Conclusion/Limitations
			95% CI) (RET; AET; WL): Physical functioning: 0 (8.16); 0.76, -0.14 to 1.67; 2.5 (7.2); 1.31, 0.34 to 2.27; -7.5 (10.3); favors AET Social functioning: 13 (13.0); -.12, -0.76 to 0.99; 10.3 (13.9); -0.01, -0.89 to 0.87; 10.5 (22.6); NS Mental health: 16.4 (16.7); 1.05, 0.11 to 1.98; 9.6 (7.4); 0.75, -0.16 to 1.65; -3.6 (10.7); favors RET **Remission rates (RET; AET; WL [%]):** 60%; 40%; 30% **AEs:** NR	

AC: active control; AEs: adverse events; BL: baseline; CI: confidence interval; ES: effect size; f/u: follow-up; mos.: months; NR: not reported; NS: not significant; RCT: randomized controlled trials; ROB: risk of bias; SD: standard deviation

Table 4. Cochrane Risk of Bias 2.0 Tool for RCTs on Exercise to Treat GAD

Reference	Herring et al. (2011)
• Was the allocation sequence generated adequately (e.g., random number table, computer-generated randomization)?	Yes
• Was the allocation of treatment adequately concealed (e.g., pharmacy-controlled randomization, concealed envelopes)?	NI
• Did baseline difference between study groups suggest a problem with randomization?	No
Overall ROB for Randomization Process	**Some concerns**
Deviation from Intended Intervention (Effect of Assignment)	
• Were participants aware of their assigned intervention during the trial?	PY
• Were providers and people delivering treatment aware of assigned intervention during trial?	PY
• Were there deviations from the intended intervention that arose because of the experimental context?	PN
• Were these deviations from intended intervention balanced between groups?	NA
• Were these deviations likely to have affected the outcome?	NA
• Was an appropriate analysis used to estimate the effect of assignment to intervention?	No
Overall ROB of Effect of Assignment	**Some Concerns**
Missing Outcome Data	
• Were data for this outcome available for all, or nearly all, participants randomized?	Yes
• Is there evidence that result was not biased by missing outcome data?	NA
• Could missingness in the outcome depend on its true value?	NA
• Do the proportions of missing outcome data differ between intervention groups?	NA
• Is it likely that missingness in the outcome depended on its true value?	NA
Overall ROB of Missing Data	**Low**
Measurement of the Outcome	
• Was the method of measuring the outcome inappropriate?	No
• Could measurement or ascertainment of the outcome have differed between intervention groups?	No
• Were outcome assessors aware of the intervention received by study participants?	PN
• Could assessment of the outcome have been influenced by knowledge of intervention received?	NA
• Is it likely that assessment of the outcome was influenced by knowledge of intervention received?	PN
Overall ROB of Measurement of Outcome	**Low**
Selection of Reported Results	

Reference	Herring et al. (2011)
• Was the trial analyzed in accordance with a pre-specified plan that was finalized before unblinded outcome data were available for analysis?	Yes
Overall ROB of Reported Results	**Low**
Overall Study ROB	**Some concerns**

*Responses: Y=Yes, PY=Probably Yes, N=No, PN=Probably No, NI=No Information; ROB: risk of bias

Table 5. Cochrane Risk of Bias 2.0 Overall Risk of Bias Judgement

Category	Definition
Low risk of bias	The study is judged to be at **low risk of bias for all domains** for this result.
Some concerns	The study is judged to be at **some concerns** in at least one domain for this result.
High risk of bias	The study is judged to be at **high risk of bias** in at least one domain for this result. OR The study is judged to have **some concerns** for **multiple domains** in a way that substantially lowers confidence in the result.

References

Herring, M. P., Jacob, M. L., Suveg, C., Dishman, R. K., & O'Connor, P. J. (2012). Feasibility of exercise training for the short-term treatment of generalized anxiety disorder: a randomized controlled trial. *Psychotherapy & Psychosomatics*, *81*(1), 21–28. https://doi.org/https://dx.doi.org/10.1159/000327898

Herring, M. P., Jacob, M. L., Suveg, C., & O'Connor, P. J. (2011). Effects of short-term exercise training on signs and symptoms of generalized anxiety disorder. *Mental Health and Physical Activity*, *4*(2), 71–77. https://doi.org/http://dx.doi.org/10.1016/j.mhpa.2011.07.002

Herring, M. P., Kline, C. E., & O'Connor, P. J. (2015). Effects of exercise on sleep among young women with Generalized Anxiety Disorder. *Mental Health and Physical Activity*, *9*, 59–66.

Herring, M. P., Johnson, K. E., & O'Connor, P. J. (2016). Exercise training and health-related quality of life in generalized anxiety disorder. *Psychology of Sport and Exercise, 27*, 138–141. https://doi.org/http://dx.doi.org/10.1016/j.psychsport.2016.08.011

Massage Therapy

Evidence Base

Our searches of the literature identified 1 RCT that met inclusion criteria. The study published by Rapaport et al. (2016) assessed the potential efficacy of Swedish massage therapy (SMT) on symptoms of anxiety among adults with clearly defined and diagnosed Generalized Anxiety Disorder (GAD). Forty-seven untreated participants were randomized to twice-weekly SMT or a light touch control group. The primary outcome of interest was reduction in Hamilton Anxiety Rating Scale (HARS) scores 6 weeks posttreatment.

Study Quality

Using the Cochrane tool, we rated the RoB of the RCT as having some concerns primarily due to no blinding of patients and high attrition. See **Table 4** for individual quality ratings.

Key Findings

Below, we describe the key findings for the outcomes of interest with the GRADE strength of the evidence (SOE) rating. See **Table 1** for factors that influenced the SOE ratings.

- Evidence from 1 RCT suggests that Swedish Massage Therapy (SMT) statistically significantly reduces symptoms of anxiety compared to active control immediately following treatment. (SOE: Low)
- Evidence from 1 RCT suggests that SMT statistically significantly reduces symptoms of depression compared to active control immediately following treatment (SOE: Low)

Discussion

Overall, the findings of the Rapaport study suggest that Swedish Massage Therapy (SMT) given twice a week statistically significantly improved clinician-rated symptoms of anxiety and depression immediately following treatment compared to an active control of light touch. However, no statistically significant differences were observed between SMT and light touch for improving self-rated anxiety symptoms. No serious adverse events were reported. The strength of the evidence for the reported outcomes was low due to methodological limitations the study including the small sample size and lack of blinding of participants.

Table 1. Strength of Evidence for Massage to Treat GAD

Outcome	Quantity and Type of Evidence	Intervention (n)/ Control (n)/Follow-up	Estimate of Effect	Study Limitations (Risk of Bias)	Inconsistency	Indirectness	Imprecision	Publication Bias	GRADE of Evidence for Outcome
Anxiety symptoms	1 RCT in Rapaport (2016)	SMT (n=23) vs. LT (n=24) 6 weeks	**Change in HARS, (SEM), 95% CI:** SMT: 11.67 (1.09); LT: 8.41 (1.01), -1.330 to -0.051; ES=-0.690, p=0.030; **favors SMT**	Yes (-1)	No	No	Yes (-1); small sample size	No	Low
Depression symptoms	1 RCT in Rapaport (2016)	SMT (n=23) vs. LT (n=24) 6 weeks	**Change in HDRS, (mean [SD]):** SMT: -9.21 (5.73); LT: -3.71 (7.12), -1.583 to 0.347; ES=-0.843, p=0.027; **favors SMT**	Yes (-1)	No	No	Yes (-1); small sample size	No	Low

CI: confidence interval; CT: control group; ES: effective size; LT: light touch; mos.: months; NR: not reported; NS: not significant; RCT: randomized controlled trials; SE: standard error; SMD: standardized mean difference; TAU: treatment as usual; WL: waitlist

Table 2. GRADE Factors Used to Assess the Quality of a Body of Evidence

Evidence Category	Definition
Study Quality (Internal Validity or Risk of Bias)	Study quality considers the overall risk of bias rating of all the studies included in the evidence base. In this review, the overall risk of bias would be the average or median USPSTF rating for studies comprising an evidence base for a key outcome.
Consistency of Evidence	Consistency of evidence refers to the degree of similarity in the direction of effects or the degree of similarity in the effect sizes (magnitude of effect) across individual studies within an evidence base.
Directness of Evidence	Direct evidence directly compares interventions of interest in populations of interest and measures patient-oriented outcomes. Evidence can be indirect if the tested intervention differs from the intervention of interest, the study population differs from the population of interest, the outcomes differ from those of primary interest, or treatment comparisons have not been tested in head-to-head comparisons.
Precision of Evidence	Precision is the degree of certainty surrounding an estimate of effect with respect to an outcome. Precision is primarily assessed by examining the 95% confidence intervals around the summary effect size.

Link to GRADE Handbook: **http://gdt.guidelinedevelopment.org/app/handbook**

Table 3. Evidence Table for RCTs on Massage to Treat GAD

Study Details	Study Population	Treatment	Results	Conclusion/Limitations
Reference: Rapaport et al. 2016 **Purpose:** To test the efficacy of a 6-wk. Swedish Massage Therapy (SMT) intervention as monotherapy for the tx. of anxiety symptoms in adults with diagnosed GAD **Setting:** NR **F/u:** 6 weeks **Funding source:** Emory University	**Number of patients:** 47; n=23 SMT; n=24 light touch control (LT) **Inclusion criteria:** Adults 18-65 years old; able to read/understand English; medically healthy; diagnosed with GAD according to DSM-IV; HAM-A score of >14; normal blood work and urinalysis **Exclusion criteria:** Individuals who lack capacity to consent; current suicidal ideation; current diagnosis of schizophrenia, bipolar disorder, borderline personality disorder; comorbid secondary diagnosis of OCD; current illicit drug use; excessive regular alcohol use; regular psychotropic medication use; current participation in psychotherapy or CBT; pregnancy; shift work schedule; active dieting for weight loss; fibromyalgia; arthritis. **Pt. baseline characteristics (SMT; LT):** **Age (mean yrs., SD):** 36.0 (13.8); 37.4 (13.1) **Gender (% female):** 81%; 78.9%	**Intervention:** SMT sessions were 45 min. twice weekly for 6 weeks. between 12pm and 6pm. At the start of each session, the study coordinator obtained information from the patient about changes in health/pregnancy status, use of prescription or OTC drugs, illicit substance use, and any new life events. Sessions were performed by licensed massage therapists from the Atlanta School of Massage who adhered to a script standardizing their interactions w/ patients and manualized tx. protocols. SMT techniques included effleurage, petrissage, and tapotement. **Control:** LT control sessions were also 45 min. twice weekly over 6 weeks and were performed by the same massage therapists and consisted of light laying on of hands in the same sequence as SMT and for the same amount of time. **Outcomes of Interest:** Anxiety symptoms (measured using the Hamilton Anxiety Rating Scale; State-Trait Anxiety Inventory); mood symptoms (Profile of Mood States); and depression symptoms (Hamilton Depression Rating Scale).	**<u>6 wks.</u>** **Anxiety symptoms (reduction in HARS [SEM], 95% CI):** SMT: 11.67 (1.09); LT: 8.41 (1.01), -1.330 to -0.051; ES=-0.690, p=0.030; favors SMT **(STAI, mean [SD]):** SMT: -14.85 (7.05); LT: -5.81 (16.81), -1.429 to 0.078; ES=-0.675, p=0.065; NS **Mood States (POMS, mean [SD]:** Tension-anxiety (SMT; LT): -4.00 (3.39); -2.18 (5.58), -1.111 to 0.347; ES=-0.382, p=0.308; NS Depression (SMT; LT): -1.77 (4.25); 1.41 (5.39), -1.386 to 0.097; ES=-0.645, p=0.091; NS **Depression symptoms (HDRS, mean [SD]):** SMT: -9.21 (5.73); LT: -3.71 (7.12), -1.583	**Conclusion:** The findings suggest that SMT statistically significantly reduces clinician-rated anxiety and depressive symptoms compared to LT control among patients receiving treatment for GAD. **Limitations:** Small sample size, limited follow-up, and attrition **Study RoB:** Low **Author conflict:** None reported

Study Details	Study Population	Treatment	Results	Conclusion/Limitations
			to 0.347; ES=-0.843, p=0.027; favors SMT **AEs:** NR	

AEs: adverse events; CI: confidence interval; f/u: follow-up; NR: not reported; NS: not significant; RCT: randomized controlled trials; RoB: risk of bias; SD: standard deviation; wks.: weeks; WL: waitlist

Table 4. Cochrane Risk of Bias 2.0 Tool for RCTs on Massage to Treat GAD

Reference	**Rapaport et al., (2016)**
• Was the allocation sequence generated adequately (e.g., random number table, computer-generated randomization)?	Yes
• Was the allocation of treatment adequately concealed (e.g., pharmacy-controlled randomization, concealed envelopes)?	Yes
• Did baseline difference between study groups suggest a problem with randomization?	No
Overall RoB for Randomization Process	**Low**
Deviation from Intended Intervention (Effect of Assignment)	
• Were participants aware of their assigned intervention during the trial?	Yes
• Were providers and people delivering treatment aware of assigned intervention during trial?	No
• Were there deviations from the intended intervention that arose because of the experimental context?	PY
• Were these deviations from intended intervention balanced between groups?	PY
• Were these deviations likely to have affected the outcome?	NA
• Was an appropriate analysis used to estimate the effect of assignment to intervention?	Yes
Overall RoB of Effect of Assignment	**Some concerns**
Missing Outcome Data	
• Were data for this outcome available for all, or nearly all, participants randomized?	No
• Is there evidence that result was not biased by missing outcome data?	Yes
• Could missingness in the outcome depend on its true value?	NA
• Do the proportions of missing outcome data differ between intervention groups?	NA
• Is it likely that missingness in the outcome depended on its true value?	NA
Overall RoB of Missing Data	**Low**
Measurement of the Outcome	
• Was the method of measuring the outcome inappropriate?	No
• Could measurement or ascertainment of the outcome have differed between intervention groups?	No
• Were outcome assessors aware of the intervention received by study participants?	No
• Could assessment of the outcome have been influenced by knowledge of intervention received?	NA
• Is it likely that assessment of the outcome was influenced by knowledge of intervention received?	NA
Overall RoB of Measurement of Outcome	**Low**
Selection of Reported Results	

Reference	Rapaport et al., (2016)
• Was the trial analyzed in accordance with a pre-specified plan that was finalized before unblinded outcome data were available for analysis?	Yes
Overall RoB of Reported Results	**Low**
Overall Study ROB	**Some concerns**

*Responses: Y=Yes, PY=Probably Yes, N=No, PN=Probably No, NI=No Information; ROB: risk of bias

Table 5. Cochrane Risk of Bias 2.0 Overall Risk of Bias Judgement

Category	Definition
Low risk of bias	The study is judged to be at **low risk of bias for all domains** for this result.
Some concerns	The study is judged to be at **some concerns** in at least one domain for this result.
High risk of bias	The study is judged to be at **high risk of bias** in at least one domain for this result. OR The study is judged to have **some concerns** for **multiple domains** in a way that substantially lowers confidence in the result.

References

Rapaport, M. H., Schettler, P., Larson, E. R., Edwards, S. A., Dunlop, B. W., Rakofsky, J. J., & Kinkead, B. (2016). Acute Swedish Massage Monotherapy Successfully Remediates Symptoms of Generalized Anxiety Disorder: A Proof-of-Concept, Randomized Controlled Study. *Journal of Clinical Psychiatry*, *77*(7), e883-91. https://doi.org/https://dx.doi.org/10.4088/JCP.15m10151

Transcranial Magnetic Stimulation (TMS)

Evidence Base

Our searches of the literature identified 3 RCTs that assessed the efficacy of TMS or repetitive (r) TMS in the treatment of adults diagnosed with Generalized Anxiety Disorder (GAD). One RCT, published by Huang et al. (2018) compared the efficacy and safety of active rTMS and sham rTMS for individuals diagnosed with GAD according to the DSM-IV as well as insomnia that had lasted 3 months or longer. Eighteen patients were randomized to each treatment group. The active rTMS was administered over the right posterior parietal cortex (PPC) at a frequency of 1 Hz and an intensity of 90% of the resting motor threshold (RMT) over the course of 10 consecutive days (3 trains of 500 pulses w/ inter-train interval of 10 min.). Sham rTMS was administered over the same area and with the same parameters as the active rTMS with the coil looking, sounding, and feeling the same, however, it did not deliver any active stimulation to the underlying cortical tissue. Patients could keep taking their SSRIs, but only if they were on a stable type and dosage for a least 3 months before trial enrollment. Follow-up was one-month post-treatment and the primary outcome was severity of anxiety symptoms.

Dilkov et al. (2017) randomized 50 individuals between the ages of 18 and 65 years with a confirmed diagnosis of GAD to receive either 6 weeks (25 treatments) of high frequency rTMS (n=15) or sham rTMS (n=25). Five individuals in the active rTMS group dropped out immediately following randomization and were not included in the analysis. Those in the active treatment group received 20 Hz at 110% intensity of the RMT to the right dorsolateral prefrontal cortex (DLPFC). All enrolled patients continued their current psychosocial or psychotropic treatments. Follow-up was 4 weeks post-treatment and the primary outcomes were change in anxiety symptoms and anxiety symptom severity. One patient in the active rTMS group experienced a generalized tonic-clonic seizure (grand mal) during the 20th rTMS treatment. All patients reported facial muscle twitching during RMT determination, and 3 patients reported transient dizziness.

Finally, an RCT published by Diefenbach et al. (2016) compared active rTMS to sham rTMS. This study randomized 25 adults with a GAD diagnosis (See **Table 4**). Concurrent pharmacotherapy was stabilized for 3 months before trial entry except for benzodiazepines as needed, which were stabilized on a daily dose for at least 2 weeks. Patients were required to keep their medication use stable over the course of the study. The active rTMS treatment was delivered at a frequency of 1 Hz for 15 minutes (900 pulses per session) with the intensity at 90% of the RMT to the right (DLPFC). The sham rTMS followed the same procedures as those used for the active rTMS, but the treatments were administered using a coil that only looked and sounded like the active coil with an intensity that was far less than the level needed to produce clinical benefit. Both active and sham interventions occurred 5 days per weeks for 6 weeks (30 sessions total; 27,000 total pulses). Follow-up was 3 months and the primary outcome was change in anxiety symptoms. See **Table 3** for more information about the patients and interventions assessed in this studies that made up the evidence base for TMS.

Study Quality

We rated the RoB of the included studies as having some concerns due to unclear information about randomization process used, lack of blinding of patients and the clinicians who provided treatment, and significant attrition (see **Table 4** for the RoB ratings of the RCTs).

Key Findings

Below, we describe the key findings for the outcomes of interest with the GRADE strength of the evidence (SOE) rating. See **Table 1** for factors that influenced the SOE ratings.

Uni-lateral TMS (any frequency) vs. Sham TMS

- Combined evidence from 3 RCTs suggest that active rTMS statistically significantly reduces anxiety symptoms compared to sham rTMS. (SOE: Low)
- Combined evidence from 3 RCTs suggest that active rTMS statistically significantly reduces depressive symptoms compared to sham rTMS (SOE: Low)
- Evidence from 1 RCT suggests that active rTMS statistically significantly reduces worry symptoms compared to sham rTMS immediately following treatment as well as at 3-months follow-up (SOE: Low)
- Evidence from 1 RCT suggests that active rTMS statistically significantly improves sleep quality compared to sham rTMS immediately following treatment as well as at 1-month follow-up (SOE: Low)

Discussion

Overall, the findings of the RCTs that made up the evidence base for rTMS suggest that active rTMS at any frequency statistically significantly reduces symptoms of anxiety, worry, and depression compared to sham rTMS. Additionally, 1 RCT found that active rTMS statistically significantly improved sleep quality compared to sham rTMS both immediately following treatment and at 1-month follow-up. Response and remission rates were also greater for patients in the active treatment group. The strength of the evidence supporting the findings for rTMS was rated as low due to methodological limitations of the included studies. Facial twitching was the most commonly reported adverse event among patients receiving active rTMS, followed by some form of pain (including neck pain, pain at stimulation site, facial pain, or toothache), a pin prick sensation, headache, or dizziness. One patient in experienced a generalized tonic-clonic seizure during the 20th rTMS treatment, however, he did fully recover and was able to complete the study.

Table 1. Strength of Evidence for Transcranial Magnetic Stimulation (TMS) to Treat GAD

Outcome	Quantity and Type of Evidence	Intervention (n)/ Control (n)/Follow-up	Estimate of Effect	Study Limitations (Risk of Bias)	Inconsistency	Indirectness	Imprecision	Publication Bias	GRADE of Evidence for Outcome
Unilateral rTMS (Any Frequency) vs Sham									
Anxiety symptoms	3 RCTs (Huang, 2018; Dilkov, 2017; Diefenbach, 2016)	rTMS (46); sham (55) 1 month reported in Huang, 2018 4 weeks reported in Dilkov, 2017 3 months reported in Diefenbach, 2016	**Change in HARS**: End of Tx (10 sessions) Active rTMS; sham (mean [SD]; % improvement; p) 11.67(5.97); 43.85%, p<0.05 18.72(4.56); 7.92%, p>0.05; **favors active rTMS** 1 mon. f/u 10.89(5.99); 47.59%, p<0.05 17.28(5.07); 15.03%, p>0.05; **favors active rTMS**	Yes (-1)	No	No	Yes (-1); small sample size	No	Low
			Change in HARS: End of tx. (25 sessions) Mean scores (± SE) from baseline (BL;	Yes (-1)	No	No	Yes (-1)	No	Low

Outcome	Quantity and Type of Evidence	Intervention (n)/ Control (n)/Follow-up	Estimate of Effect	Study Limitations (Risk of Bias)	Inconsistency	Indirectness	Imprecision	Publication Bias	GRADE of Evidence for Outcome
			visit[v] 1), weeks 2–6 of treatment (v2–v4) to the follow-up phase, weeks 8 and 12 (v5–6) with a significant difference (*) at week 4(v3), t (38) = 5.74, p < 0.001, week 6 (v4), t (38) = 8.50, p < 0.001; **favors active rTMS** 4 wks. f/u week 8 (v5), t (38) = 10.8, p < 0.001 and week 12 (v6), t (38) = 10.7, p < 0.001; **favors active rTMS**						
			Change in HARS: End of tx. (6 wks) active rTMS; sham (mean	Yes (-1)	No	No	Yes (-1); small sample size	No	Low

Outcome	Quantity and Type of Evidence	Intervention (n)/ Control (n)/Follow-up	Estimate of Effect	Study Limitations (Risk of Bias)	Inconsistency	Indirectness	Imprecision	Publication Bias	GRADE of Evidence for Outcome
			[SD], ES; 95% CI, p) 12.10(5.77); ES=1.91; 0.97 to 2.83, p<0.001 14.38(4.78); ES=1.47; 0.63 to 2.29, p<0.001; **NS difference between the two grps. Both active and sham experienced large and statistically significant improvements** 3 mos. f/u 10.36(7.86); ES= 1.61; 0.76 to 2.43, p<0.001 17.95(7.48); ES=0.37; -0.23 to 0.95, p>0.05; **favors active rTMS**						

Outcome	Quantity and Type of Evidence	Intervention (n)/ Control (n)/Follow-up	Estimate of Effect	Study Limitations (Risk of Bias)	Inconsistency	Indirectness	Imprecision	Publication Bias	GRADE of Evidence for Outcome
Depression symptoms	3 RCTs (Huang, 2018; Dilkov, 2017; Diefenbach, 2016)	rTMS (46); sham (55) 1 month reported in Huang, 2018 4 weeks reported in Dilkov, 2017 3 months reported in Diefenbach, 2016	**Change in HRSD:** Post-tx. active rTMS; sham (mean [SD]; % improvement; p) 8.61(3.79); 34.6, p<0.05 12.22(3.7); 6.38%, p>0.05; **favors active rTMS** 1 mon. f/u 7.33(4.3); 44.3%, p<0.05 11.11(2.97); 14.89%, p>0.05; **favors active rTMS**	Yes (-1)	No	No	Yes (-1); small sample size	No	Low
			Change in HRSD: Post-tx mean [SD], p 4(1); 14(6), p<0.001; **favors active rTMS** 4 wks. f/u 4(1); 15(4), p<0.001;	Yes (-1)	No	No	Yes (-1); small sample size	No	Low

Outcome	Quantity and Type of Evidence	Intervention (n)/ Control (n)/Follow-up	Estimate of Effect	Study Limitations (Risk of Bias)	Inconsistency	Indirectness	Imprecision	Publication Bias	GRADE of Evidence for Outcome
			favors active rTMS						
			<u>Change in HRSD:</u> Post-tx active rTMS; sham mean [SD], ES; 95% CI, p 9.30(4.39); ES=1.16; 0.44 to 1.86, p<0.01 11.40(3.52); ES=0.62; -0.01 to 1.23, p>0.05; **favors active rTMS** 3 mos. f/u 7.78(5.38); ES=1.12; 0.41 to 1.81, p<0.01 13.40(5.68); ES=-0.08; -1.04 to 0.87, p>0.05; **favors active rTMS**	Yes (-1)	No	No	Yes (-1); small sample size	No	Low
Worry symptoms	1 RCT (Diefenbach, 2016)	rTMS (13) vs sham (12) F/u: 3 mos.	**<u>Change in PSWQ:</u>** Post-tx active rTMS; sham (mean	Yes (-1)	No	No	Yes (-1); small sample size	No	Low

Outcome	Quantity and Type of Evidence	Intervention (n)/ Control (n)/Follow-up	Estimate of Effect	Study Limitations (Risk of Bias)	Inconsistency	Indirectness	Imprecision	Publication Bias	GRADE of Evidence for Outcome
			[SD], ES; 95% CI, p) 61.73(8.80); ES= 0.72; 0.09 to 1.32, p<0.05 61.77(8.35); ES=0.07; -0.50 to 0.63, p>0.05; **favors active rTMS** 3 mos. 54.36(8.10); ES=1.35; 0.57 to 2.09, p<0.001 57.49(8.85); ES=0.62; -0.01 to 1.23, p>0.05; **favors active rTMS**						
Sleep quality	1 RCT (Hunag, 2018)	rTMS (18) vs sham (18) F/u: 1 mos.	**Change in PSQI:** Post-tx. active rTMS; sham (mean [SD]; % improvement; p) 7.06(2.75); 44.05%, p<0.05	Yes (-1)	No	No	Yes (-1); small sample size	No	Low

Outcome	Quantity and Type of Evidence	Intervention (n)/ Control (n)/Follow-up	Estimate of Effect	Study Limitations (Risk of Bias)	Inconsistency	Indirectness	Imprecision	Publication Bias	GRADE of Evidence for Outcome
			11.44(4.13); 12.34%, p>0.05; **favors active rTMS** 1 mos. f/u 7.28(3.37); 42.29%, p<0.05 11.56(3.82); 11.49%, p>0.05; **favors active rTMS**						

CI: confidence interval; f/u: follow-up; mos.: months; NA: not applicable; NR: not reported; NS: not significant; RCT: randomized controlled trials; rTMS: repetitive TMS; SD: standard deviation; SMD: standardized mean difference; TMS: transcranial magnetic stimulation

Table 2. GRADE Factors Used to Assess the Quality of a Body of Evidence

Evidence Category	Definition
Study Quality (Internal Validity or Risk of Bias)	Study quality considers the overall risk of bias rating of all the studies included in the evidence base. In this review, the overall risk of bias would be the average or median USPSTF rating for studies comprising an evidence base for a key outcome.
Consistency of Evidence	Consistency of evidence refers to the degree of similarity in the direction of effects or the degree of similarity in the effect sizes (magnitude of effect) across individual studies within an evidence base.
Directness of Evidence	Direct evidence directly compares interventions of interest in populations of interest and measures patient-oriented outcomes. Evidence can be indirect if the tested intervention differs from the intervention of interest, the study population differs from the population of interest, the outcomes differ from those of primary interest, or treatment comparisons have not been tested in head-to-head comparisons.
Precision of Evidence	Precision is the degree of certainty surrounding an estimate of effect with respect to an outcome. Precision is primarily assessed by examining the 95% confidence intervals around the summary effect size.

Link to GRADE Handbook: **http://gdt.guidelinedevelopment.org/app/handbook**

Table 3. Evidence Table for RCTs on Transcranial Magnetic Stimulation (TMS) to Treat GAD

Study Details	Study Population	Treatment	Results	Conclusion/Limitations
Reference: Huang et al. 2018 **Purpose:** Randomized trial to compare the efficacy of rTMS to sham for GAD. **Setting:** Xuanwu Hospital, China **Funding source:** Natural Science Foundation of China, Grant No. 81300138 and the National High-Tech R&D Program of China (863 Program), Grant No. 2015AA020514	**Number of patients:** 36; n=18 active rTMS; n=18 sham rTMS **Inclusion criteria:** Aged 18 to 65; diagnosed with GAD; diagnosed with insomnia related to another mental disorder with duration of insomnia ≥ 3 mos., and scored ≥ 14 on HRSA, ≥ 7 on the PSQI, and < 20 on the 24-item HRSD-24; concurrent SSRIs permitted but only if at stable type and dosage for at least 3 mos. prior to trial enrollment (participants required to keep medication stable throughout study); concurrent use of short half-life benzodiazepines w/ limited dose were permitted (but frequency exceeding 3 times/wk. was not allowed) **Exclusion criteria:** Prior history of other psychiatric diseases including all types of anxiety disorders other than GAD, and substance or alcohol abuse or dependence; evidence of neurological or other physical diseases such as respiratory, cardiac, renal, hepatic, and endocrinal diseases as assessed by clinical history, physical examination, or routine lab tests; pregnancy or breastfeeding women; any contraindication for rTMS; concurrent psychotherapy or counseling	**Intervention:** unilateral rTMS consisting of 3 trains of 500 pulses w/ an inter-train interval of 10 min., administered daily for 10 consecutive days. **Control:** Sham rTMS using similar equipment but without active stimulation for 10 daily sessions. **Outcomes:** Anxiety levels (HRSA); sleep quality (PSQI); depressive symptoms (HRSD-24) **F/u:** 1 month	**End of Tx (10 sessions)** HRSA, active rTMS; sham (mean [SD]; % improvement; p) 11.67(5.97); 43.85%, p<0.05 18.72(4.56); 7.92%, p>0.05; **favors active rTMS** PSQI, active rTMS; sham (mean [SD]; % improvement; p) 7.06(2.75); 44.05%, p<0.05 11.44(4.13); 12.34%, p>0.05; **favors active rTMS** HRSD, active rTMS; sham (mean [SD]; % improvement; p) 8.61(3.79); 34.6, p<0.05 12.22(3.7); 6.38%, p>0.05; **favors active rTMS** **1 Month F/u** HRSA, active rTMS; sham (mean [SD]; % improvement, p) 10.89(5.99); 47.59%, p<0.05 17.28(5.07); 15.03%, p>0.05; **favors active rTMS**	Results suggest that unilateral active rTMS administered to the right parietal lobe statistically significantly reduced symptoms of anxiety, insomnia, and depression compared to sham rTMS after 10 sessions of treatment with only mild AEs reported. **Limitations:** Small sample size **Study ROB:** Some concerns due to lack of information around randomization, allocation concealment, and blinding of patients and clinicians **Author conflict:** None reported

Study Details	Study Population	Treatment	Results	Conclusion/Limitations
	Pt. baseline characteristics (rTMS; sham): Age (mean yrs [SD]): 44.94 (11.64); 45.22 (10.85) Gender (male: female): 9:9; 9:9 Drug naïve/medicated pts.: 7/11; 8/10 Disease duration (mean yrs. [SD]): 4.69 (4.77); 3.72 (4.65)		PSQI, active rTMS; sham (mean [SD]; % improvement, p) 7.28(3.37); 42.29%, p<0.05 11.56(3.82); 11.49%, p>0.05; **favors active rTMS** HRSD, active rTMS; sham (mean [SD]; % improvement, p) 7.33(4.3); 44.3%, p<0.05 11.11(2.97); 14.89%, p>0.05; **favors active rTMS** **AEs:** No serious adverse events; mild headaches (active rTMS, n=5; sham, n=3), and neck pain (active, n=6; sham, n=4) were reported by subsided post-tx.	
Reference: Dilkov et al. 2017 **Purpose:** Randomized trial to test if rTMS would improve clinical outcomes compared to sham for patients with GAD who had failed to respond to first-line pharmacotherapy **Setting:** NR **Funding source:** Queen's University;	**Number of patients:** 50 (n=15 active rTMS; n=25 sham rTMS) **Inclusion criteria:** Signed patient informed consent; primary GAD diagnosis; HARS ≥15; male or female aged 18-65; w/o GAD pharmacotherapy at least last 2 wks., or if taking GAD medication, it must be stable for at least 6 wks. prior to study start and not be changed during the 6 wks. of the study tx. phase; individual or group supportive psychotherapy may continue during the study but not allowed	**Intervention:** High frequency unilateral rTMS (20 Hz, 110% RMT for 20 trains, 9 sec. per train, 51 sec. intertrain intervals) to the right DLPFC for 5 sessions a week for the first 4 weeks; during the 5th week, sessions were reduced to 3 times per week and again to 2 times per week during the 6th week **Control:** Sham rTMS; same as above without active stimulation	**Posttreatment (25 sessions)** **Anxiety symptoms** HARS mean scores (± SE) from baseline (BL; visit[v] 1), weeks 2–6 of treatment (v2–v4) to the follow-up phase, weeks 8 and 12 (v5–6) with a significant difference (*) at week 4(v3), t (38) = 5.74, p < 0.001, week 6 (v4), t (38) = 8.50, p < 0.001; **favors active rTMS**	Results suggest that anxiety and depressive symptoms improved from BL to follow-up and reached statistical significance in the active rTMS group **Limitations:** Lack of blinding; small sample size **Study ROB:** Some concerns **Author conflict:** None reported

Study Details	Study Population	Treatment	Results	Conclusion/Limitations
Military Medical Academy	to start new psychotherapy group during the 6 wks. of the study tx. phase **Exclusion criteria:** Current serious Axis I schizophrenia, bipolar I, MDD; other primary Axis I in the opinion of investigator; HDRS ≥18; metallic implant in cranium except mouth; severe/unstable medical conditions; ECT within last 3 mos.; epilepsy history; neurological disorder leading to increased intracranial pressure; current suicide risk **Pt. baseline characteristics (active rTMS; sham rTMS):** Age (mean yrs. [SD]): 34(7); 38(10) Gender (% male): 22%; 30% Not taking medication (n): 6; 11 Taking ≥ 2 medications by type: SSRIs: 4; 8 SNRIs: 4; 5 SARIs: 0; 2 Atypical antidepressants: 1; 2 Benzodiazepines: 1; 2 Non-benzodiazepine hypnotics: 3; 4 Tricyclic antidepressants: 1; 0 Typical antipsychotics: 0; 5 Atypical antipsychotics: 2; 2 Antiparkinson's anticholinergics: 0; 1	**Outcomes of Interest:** Anxiety symptoms measured by Hamilton Anxiety Rating Scale (HARS), symptom severity measured by Clinical Global Impression Scale (CGI), and depressive symptoms measured by Hamilton Depression Rating Scale (HDRS-21) **F/u:** 4 weeks posttreatment	**Depressive symptoms** (active rTMS; sham) HDRS-21 (mean [SD], p) 4(1); 14(6), p<0.001; **favors active rTMS** **Symptom severity** (active rTMS; sham) CGI (mean [SD], p) 3(0.5); 5(1), p<0.001; **favors active rTMS** **2 and 4 wks. f/u** **Anxiety symptoms** HARS mean score (± SE) week 8 (v5), t (38) = 10.8, p < 0.001 and week 12 (v6), t (38) = 10.7, p < 0.001; **favors active rTMS** **Depressive symptoms** (active rTMS; sham) HDRS-21 (mean [SD], p) 4(1); 15(4), p<0.001; **favors active rTMS** **Symptoms severity** (active rTMS; sham) CGI (mean [SD], p) 2(0.5); 5(1), p<0.001; **favors active rTMS**	

Study Details	Study Population	Treatment	Results	Conclusion/Limitations
	Anticonvulsants: 0; 2 Melatonergic antidepressants: 1; 0 Melatonin: 1; 1		**AEs:** 1 patient in the active rTMS grp. experienced a generalized tonic-clonic seizure during the 20th rTMS tx. For the duration of the study, he was receiving escitalopram, trazodone, and melatonin; no other significant medical history or use of other substances prior to seizure reported. The patient fully recovered and finished the study. All patients reported facial muscle twitching during RMT determination; 3 pts. reported transient dizziness	
Reference: Diefenbach et al. 2016 **Purpose:** Randomized trial to test the efficacy and neural correlates of rTMS in GAD **Setting:** Hartford Hospital **Funding source:** Hartford Hospital; Neuronetics	**Number of patients:** 25 (n=13 active rTMS; n=12 sham rTMS) **Inclusion criteria:** Diagnosis of GAD; Clinical Global Impression score ≥ 4; Hamilton Anxiety Rating Scale ≥ 18; Hamilton Rating Scale for Depression ≤ 17; fluent in English; capacity to understand the nature of the study and willingness to sign informed consent form **Exclusion criteria:** History of epilepsy or head trauma (LOC > 5 min.) within past 6 mos.; lifetime history of increased intracranial pressure, seizure disorder, stroke, brain tumor, multiple sclerosis, or brain surgery; an active autoimmune, endocrine, viral, or vascular disorder affecting the brain; any unstable cardiac	**Intervention:** rTMS delivered at frequency of 1Hz for 15 min. (900 pulses/session) with intensity at 90% RMT to the right DLPFC, for 30 sessions (5 days/week for 6 weeks; 27,000 total pulses) **Control:** Sham rTMS; same as above but with intensity of the magnetic stimulus far below the level needed to produce clinical benefit **Outcomes of Interest:** Anxiety symptoms measured by Hamilton Anxiety Rating Scale (HARS); self-reported worry measured with Penn State Worry Questionnaire (PWSQ); clinician-rated depression measured with HRSD; Responder status	**<u>Posttreatment (6 wks.)</u>** **Anxiety symptoms** HRSA, active rTMS; sham (mean [SD], ES; 95% CI, p) 12.10(5.77); ES=1.91; 0.97 to 2.83, p<0.001 14.38(4.78); ES=1.47; 0.63 to 2.29, p<0.001; **NS difference between the two grps. Both active and sham experienced large and statistically significant improvements** **Worry symptoms** PSWQ, active rTMS; sham (mean [SD], ES; 95% CI, p) 61.73(8.80); ES= 0.72; 0.09 to 1.32, p<0.05	Results suggest that active rTMS may be more effective than sham in achieving statistically significant response and remission status among patients with GAD than sham rTMS both immediately following treatment as well as at 3 months follow-up. While patients in both the active and sham groups both experienced large and statistically significant improvements in anxiety symptoms immediately following treatment, only those in the active rTMS group maintained that improvement at follow-up. Patients in active rTMS also demonstrated statistically significant improvements in worry and depressive symptoms

Study Details	Study Population	Treatment	Results	Conclusion/Limitations
	disease; hypertension; or several renal or liver insufficiency; substance use disorder or PTSD within past 6 mos.; lifetime bipolar disorder, OCD, psychotic disorder, mental retardation, or pervasive developmental disorder; any psychotic features including dementia or delirium; concurrent psychotherapy and unwillingness to discontinue; medication change in past 3 mos.; current serious suicidal or homicidal ideation, and/or serious suicidal attempt in past 6 mos.; serious, unstable, or terminal medical condition or clinically judged too psychiatrically unstable to participate in study; any contradiction for participation in MRI scan. **Pt. baseline characteristics (active rTMS; sham rTMS):** Age (mean yrs. [SD]): 44(11.95); 44.58(14.75) Gender (% female): 84.6%; 66.7% Taking psychotropic medication (%): 69.2%; 66.7%	defined as ≥50% HRSA improvement; Remission status defined as HRSA <8 and a CGI-I score of 1 (very much improved) or 2 (much improved) **F/u:** 3 months	61.77(8.35); ES=0.07; -0.50 to 0.63, p>0.05; **favors active rTMS** **Depressive symptoms** HRSD, active rTMS; sham (mean [SD], ES; 95% CI, p) 9.30(4.39); ES=1.16; 0.44 to 1.86, p<0.01 11.40(3.52); ES=0.62; -0.01 to 1.23, p>0.05; **favors active rTMS** **Responder status:** active = 61.5%; sham = 16.7%, p=0.022; **favors active rTMS** **Remitter status:** active = 30.8%; sham = 8.3%, p=0.161; **NS** **<u>3 Months F/u</u>** **Anxiety symptoms** HRSA, active rTMS; sham (mean [SD]; ES; 95% CI, p) 10.36(7.86); ES= 1.61; 0.76 to 2.43, p<0.001 17.95(7.48); ES=0.37; -0.23 to 0.95, p>0.05; **favors active rTMS** **Worry symptoms**	immediately following treatment and maintained those improvements at 3 months follow-up. **Limitations:** Small sample size; high attrition rates; randomization schedule did not equally distribute anxiety symptoms leading to patients with more severe anxiety being allocated to active rTMS **Study ROB:** Some concerns **Author conflict:** None reported

Study Details	Study Population	Treatment	Results	Conclusion/Limitations
			PSWQ, active rTMS; sham (mean [SD], ES; 95% CI, p) 54.36(8.10); ES=1.35; 0.57 to 2.09, p<0.001 57.49(8.85); ES=0.62; -0.01 to 1.23, p>0.05; **favors active rTMS** **Depressive symptoms** HRSD, active rTMS; sham (mean [SD], ES; 95% CI, p) 7.78(5.38); ES=1.12; 0.41 to 1.81, p<0.01 13.40(5.68); ES=-0.08; -1.04 to 0.87, p>0.05; **favors active rTMS** **Responder status:** active = 61.5%; sham = 0%, p=0.001; **favors active rTMS** **Remitter status:** active = 53.8%; sham = 0%, p=0.003; **favors active rTMS** **AEs:** Pin prick sensation was reported by 9 patients in the active grp. and 10 patients in the sham grp. Pain at the stimulation site was reported by 11 patients in the active grp. and 8 patients in the sham grp. Facial pain was reported by 3 patients in the active grp. and 1	

Study Details	Study Population	Treatment	Results	Conclusion/Limitations
			patient in the sham grp. Headache was reported by 6 patients in the active grp. and 3 patients in the sham grp. Toothache was reported by 3 patients in the active grp. Lightheaded dizziness was reported by 2 patients in the sham grp. Facial twitch was reported by 6 patients in the active grp.	

AEs: adverse events; BL: baseline; CI: confidence interval; DLPFC: dorsolateral prefrontal cortex; f/u: follow-up; mos.: months; NR: not reported; NS: not significant; RCT: randomized controlled trials; ROB: risk of bias; rTMS: repetitive transcranial magnetic stimulation; SD: standard deviation; TMS: transcranial magnetic stimulation

Table 4. Cochrane Risk of Bias 2.0 Tool for RCTs on TMS to Treat GAD

Reference	Huang et al., (2018)	Dilkov et al., (2017)	Diefenbach et al., (2016)
• Was the allocation sequence generated adequately (e.g., random number table, computer-generated randomization)?	NI	Yes	Yes
• Was the allocation of treatment adequately concealed (e.g., pharmacy-controlled randomization, concealed envelopes)?	NI	Yes	Yes
• Did baseline difference between study groups suggest a problem with randomization?	No	No	No
Overall RoB for Randomization Process	**Some Concerns**	**Low**	**Low**
Deviation from Intended Intervention (Effect of Assignment)			
• Were participants aware of their assigned intervention during the trial?	PN	PN	PN
• Were providers and people delivering treatment aware of assigned intervention during trial?	PN	PN	PN
• Were there deviations from the intended intervention that arose because of the experimental context?	No	No	No
• Were these deviations from intended intervention balanced between groups?	NA	NA	NA
• Were these deviations likely to have affected the outcome?	NA	NA	NA
• Was an appropriate analysis used to estimate the effect of assignment to intervention?	No	NA	NA
Overall RoB of Effect of Assignment	**Some Concerns**	**Some Concerns**	**Some concerns**
Missing Outcome Data			
• Were data for this outcome available for all, or nearly all, participants randomized?	Yes	No	Yes
• Is there evidence that result was not biased by missing outcome data?	Yes	Yes	Yes
• Could missingness in the outcome depend on its true value?	NA	NA	NA
• Do the proportions of missing outcome data differ between intervention groups?	NA	NA	NA
• Is it likely that missingness in the outcome depended on its true value?	NA	NA	NA
Overall RoB of Missing Data	**Low**	**Low**	**Low**
Measurement of the Outcome			
• Was the method of measuring the outcome inappropriate?	No	No	No
• Could measurement or ascertainment of the outcome have differed between intervention groups?	No	No	No

Reference	Huang et al., (2018)	Dilkov et al., (2017)	Diefenbach et al., (2016)
• Were outcome assessors aware of the intervention received by study participants?	No	No	No
• Could assessment of the outcome have been influenced by knowledge of intervention received?	NA	NA	NA
• Is it likely that assessment of the outcome was influenced by knowledge of intervention received?	NA	NA	NA
Overall RoB of Measurement of Outcome	**Low**	**Low**	**Low**
Selection of Reported Results			
• Was the trial analyzed in accordance with a pre-specified plan that was finalized before unblinded outcome data were available for analysis?	NI	Yes	Yes
Overall RoB of Reported Results	**Some Concerns**	**Low**	**Low**
Overall Study RoB	**Some concerns**	**Some concerns**	**Some concerns**

*Responses: Y=Yes; PY=Probably Yes; N=No; PN=Probably No; NA=Not Applicable; NI=No Information; RoB: risk of bias

Table 8. Cochrane Risk of Bias 2.0 Overall Risk of Bias Judgement

Category	Definition
Low risk of bias	The study is judged to be at **low risk of bias for all domains** for this result.
Some concerns	The study is judged to be at **some concerns** in at least one domain for this result.
High risk of bias	The study is judged to be at **high risk of bias** in at least one domain for this result. OR The study is judged to have **some concerns** for **multiple domains** in a way that substantially lowers confidence in the result.

References

Diefenbach, G. J., Bragdon, L. B., Zertuche, L., Hyatt, C. J., Hallion, L. S., Tolin, D. F., … Assaf, M. (2016). Repetitive transcranial magnetic stimulation for generalised anxiety disorder: A pilot randomised, double-blind, sham-controlled trial. *British Journal of Psychiatry*, *209*(3), 222–228. https://doi.org/https://dx.doi.org/10.1192/bjp.bp.115.168203

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Relaxation Techniques

Evidence Base

Our searches of the literature identified 5 RCTs that met inclusion criteria and assessed the efficacy of relaxation therapy (RT). Dugas et al. (2010) conducted an RCT in which 65 patients were randomized to receive 12 weeks of cognitive-behavioral therapy (CBT, n=23), applied relaxation (AR, n=22), or waitlist (WL, n=20). The patients were 43 women and 22 men and had a mean age of 38.5±12 years. **Table 3** presents more information about the characteristics of the enrolled patients. The primary outcomes of interest in the RCT were overall severity of GAD, symptoms of pathological worry, somatic symptoms, state-trait anxiety symptoms, depressive symptoms, and global clinical improvement. Cognitive-behavioral therapy (CBT) consisted of 12 weekly 1-hour sessions and covered the following treatment phases: psychoeducation and worry awareness training, uncertainty recognition and behavioral exposure, reevaluation of the usefulness of worry, problem-solving training and imaginal exposure. Similarly applied relaxation (AR) were matched to conduct 12 weekly 1-hour therapy sessions covering the following treatment phases: psychoeducation and tension awareness training, tension-release training, relaxation by recall, relaxation by counting, and conditioned relaxation. Wait-listed participants were contacted by telephone every three weeks by the psychiatrist to monitor their state. Patients in the waitlist group were delayed entry to an active intervention group for 12 weeks but completed the same outcome assessments as those in the intervention groups.

Hayes-Skelton et al. (2013) conducted an RCT in which 81 individuals were randomized to receive 16 sessions of either an acceptance-based behavior therapy (ABBT=40) or applied relaxation (AR= 41). The patients were 65.4% female, 80.2% identified as White with an average age 32.92. **Table 3** presents more information about the characteristics of the enrolled patients. The primary outcomes of interest in the RCT were overall severity of anxiety, pathological worry, anxiety, depression, and quality of life. Participants in both the ABBT and AR groups received 16 sessions, with four initial weekly 90-min sessions followed by weekly 60-min sessions and a biweekly taper between Sessions 14, 15, and 16. ABBT focuses on modifying problematic relationships with one's internal experiences, while decreasing experiential avoidance and behavioral constriction. Each session began with a mindfulness exercise and a review of between session assignments, followed by the session-specific content, and ending with the assignment of between-session activities. ABBT had two distinct phases of treatment. The first phase (roughly Sessions 1–7) introduced clients to an acceptance-based behavioral model of anxiety. Sessions in the second phase (roughly Sessions 8–16) focused on applying the mindfulness and acceptance skills developed in the first phase of therapy as the client pursues valued life directions. AR focused on developing relaxation skills primarily through diaphragmatic breathing and progressive muscle relaxation (PMR; moving from 16 muscle groups gradually to a rapid relaxation that can be applied in daily life); enhancing awareness of early signs of anxiety; and finally applying a brief relaxation exercise in response to early signs of anxiety. In the first half of AR (roughly Sessions 1–8), the focus was on building relaxation skills and developing an awareness of client-specific early signs of anxiety. The second phase of therapy (roughly Sessions 8–16) focused on applying relaxation to early signs of anxiety both in session and between session.

Janbozorgi et al. (2009) conducted an RCT in which 32 patients were randomized to receive 12 weeks of integrative relaxation training (IRT, n=17), or control (n=15). The mean age of the participants was

24.64±3.77 years; 35% were married and 87.5% were women. **Table 3** presents more information about the characteristics of the enrolled patients. The interventions applied during the treatment period included 12-weeks of IRT: a combination of progressive relaxation training, a lifestyle relaxation program (e.g. organization of sleep time, healthy eating, exercise), and spiritual exercises (e.g. meditation, prayer). Each session was attended by participants in groups of 10–15 persons, lasted for about 1.5 to 2 hours and was divided into 4 sections: review of homework, relaxation training, discussion of lifestyle and spiritual dimensions. The control group completed the questionnaires but did not take part in the interventions.

Hoyer et al. (2009) conducted a study in which 73 patients received one of the two active treatments, worry exposure (WE) or applied relaxation (AR) as an adjunct treatment to pharmacotherapy. Patients were randomized to receive 15 sessions of therapy (WE, n=24), applied relaxation (AR, n=18) or waitlist (n = 31). Then during a second randomization after 15 weeks, the waitlist (WL, n=31) participants were allocated making the total number of patients equal to 36 in WE and 32 in the AR group. Most of the participants were female (n = 52; 71%), with the mean age of 45.4 ± 12.48 years. **Table 3** presents more information about the characteristics of the enrolled patients. The primary outcomes of interest in the RCT were anxiety and depression symptoms, including excessive worrying, negative metacognitive appraisal of worrying and thought suppression. The AR treatment commenced with psychoeducation. Beginning with progressive muscle relaxation, the patients were trained in different steps of relaxation procedures during the subsequent 6–7 sessions. The patients then applied their relaxation skills whenever signals of tension, worrying or anxiety occurred in daily life. There was no explicit confrontation instruction, although transfer to everyday situations was encouraged at the end of treatment (sessions 14 and 15). The treatment was completed with relapse prevention. Worry exposure (WE) is a core element of cognitive- behavioral treatment for GAD. This is the first randomized control trial of WE as a stand-alone treatment for GAD. The WE treatment also began with psychoeducation but explained the disorder using concepts of avoidance. The treatment commenced with self-monitoring of worry. WE began in the 3rd session and continued through the 10th. The final stage of therapy targeted generalization and relapse prevention. In both treatment conditions, the patients were assigned homework exercises. Patients in the waitlist group were delayed entry to an active intervention group for 15 weeks but completed the same outcome assessments as those in the intervention groups.

Conrad et al. (2008) conducted an RCT in which 49 patients were randomized to receive 12 weeks of applied relaxation (AR or WLC[2]: n=49); and NAC[3] (n=21) as an adjunct treatment to pharmacotherapy. The patients were men (GAD 43%; NAC 38%) and women (GAD 57%; NAC 62%) with a mean age of 43-46 years. **Table 3** presents more information about the characteristics of the enrolled patients. The primary outcomes of interest in the RCT were anxiety, worry, stress, cognitive and somatic anxiety symptoms, and depressive symptoms. The goal of AR is to teach the patient to drastically reduce muscle tension at times of stress or anxiety. Therapy was standardized, consisting of 12 weekly sessions lasting for 50 to 60 min and homework. Patients were treated individually. In Session 1, the therapist explained the treatment rationale and gave homework assignments to self-observe and record early anxiety signals. The relaxation training started with the classic tension–release cycles in Sessions 2 and 3, but in Session 4, the therapist changed the instruction to do only the release part of the cycle. In Session 5, the therapist introduced cue-controlled relaxation, which links the self-instruction to relax and the state of being

[2] Waitlist control
[3] Non-anxious control

relaxed by conditioning. In Sessions 6 and 7, the patient practiced relaxing in different situations without tensing muscles not used for posture or movement at the particular moment (differential relaxation). Rapid relaxation was taught in Session 8, with the goal of reducing the time taken to relax to 20 to 30 s. Session 9 was used for a review of all techniques, before the therapist moved on to in vivo and in sensu application training in Sessions 10 and 11. Finally, Session 12 completed the treatment with maintenance instructions. Each therapy session was audiotaped for quality assurance. Sessions with a physiological assessment scheduled before them (Sessions 2, 5, and 10) were exceptions in that, after Session 1, 4, and 9, there had to be at least 1 week of practice before assessment took place. The WLC group did not wait to complete a follow-up assessment when the AR did, but began treatment immediately after the fifth Relaxation Test.

Study Quality

Using the Cochrane tool, we rated the RoB of the RCTs by Dugas and Hayes-Skelton as having some concerns and the RoB of the RCTs by Janbozorgi, Hoyer, and Conrad as high due to lack of information about allocation concealment, lack of blinding of providers, and high attrition rates. See Error! Reference source not found.**4** for study quality ratings.

Key Findings

Below, we describe the key findings for the outcomes of interest with the GRADE strength of the evidence (SOE) rating. See **Table 1** for factors that influenced the SOE ratings.

- Evidence from 1 RCT suggests that AR statistically significantly reduces overall severity of GAD posttest compared to waitlist. (SOE: Low)
- Evidence from 1 RCT suggests that CBT and AR are statistically significantly equivalent in all outcomes at posttreatment and at 6-,12-,24 months follow-up, but CBT (and not AR) appears to lead to continued improvement over the 2 years following the end of treatment. (SOE: Low)
- Evidence from 1 RCT suggests that IRT was superior to control in reducing symptoms of anxiety at statistically significant levels (SOE: Very low)
- Evidence from 1 RCT suggests that IRT was superior to control in achieving emotional stability, relaxation, venturesome and decreasing worry at statistically significant levels indicating improved quality of life and functional status (SOE: Very low)
- Evidence from 1 RCT suggests that clinician-rated severity of GAD and symptoms of anxiety, worry, depression, and quality of life all improved posttreatment and at 6 months follow-up, but there was no statistically significant difference between ABBT and AR (SOE: Moderate)
- Evidence from 1 RCT suggests a statistically significant difference in diagnostic change, responder status, and high end-state functioning at posttreatment for both ABBT (63.3–80.0%) and AR (60.6–78.8%) as well as at 6 months follow-up (ABBT; 66.7–80.0%) (AR; 60.6–78.8%) (SOE: Moderate)
- Evidence from 1 RCT suggests that ABBT and AR are comparably credible and acceptable to participants, indicating the patient satisfaction was similar between both treatments. (SOE: Moderate)

- Evidence from 1 RCT suggests that both AR and WE statistically significantly improve overall severity of anxiety, global anxiety symptoms, overall severity-of-illness, depressive symptoms at posttest (SOE: Moderate)
- Evidence from 1 RCT suggests that both AR and WE statistically significantly improve pathological worry at posttest, and WE maintained improvement in worry symptoms significantly at 6- and 12 months follow-up. (SOE: Low-Moderate)
- Evidence from 1 RCT suggests that the proportion of patients reaching high end state functioning at posttest are 48% in WE and 56% in AR. (SOE: Moderate)
- Evidence from 1 RCT suggests that the proportion of patients responding to treatment at posttest are 45% in WE and 47% in AR. (SOE: Moderate).
- Evidence from 1 RCT suggests that there were significant self-ratings of anxiety symptoms, worry symptoms, and perceived stress, with the AR group improving more than the waitlist group at posttreatment in all these primary outcome measures. There was a trend toward ratings of worsening anxiety (significant) and worsening of stress and worry (nonsignificant) in AR at 6 weeks follow-up. (SOE: Moderate)
- Evidence from 1 RCT suggests that there was significant improvement in measured anxiety symptoms (BAI), worry symptoms (PSWQ), and perceived stress (PSS), with the AR group improving more than the WLC group at posttreatment in all these primary outcome measures. There was a significant trend towards worsening anxiety symptoms, but continued improvement in stress and worry symptoms in AR at 6 weeks follow-up. (SOE: Moderate)
- Evidence from 1 RCT suggests that there was more improvement in AR than in the WLC group in secondary measures like cognitive and somatic anxiety (CSAI), but not in depression symptoms (BDI) at posttreatment. (SOE: Moderate).

Discussion

The evidence base consists of five randomized control trials that assessed the efficacy of the relaxation therapy for treating generalized anxiety disorder (GAD). Data suggests that enrolled patients across five trials were mostly women (57%-88%) with a diagnosed GAD, in the age range of 20-50 years. Patients were recruited at various settings e.g. clinics/psychotherapy units, universities, and healthcare systems. The studies compared the efficacy of different forms of relaxation therapies e.g. Applied Relaxation (AR) or Integrative Relaxation Training (IRT) to another active treatment (CBT, ABBT, and WE). A couple of the studies also included a wait-list control condition to confirm each treatment's efficacy. Overall, the results suggested that applied relaxation therapy (AR) through mind-body exercises is equally efficacious as CBT and ABBT. These treatments are comparably credible and acceptable to participants. The studies looked at the following outcomes: symptoms of anxiety, worry, depression, emotional stability, somatic symptoms, cognitive symptoms, clinical global improvement, quality of life, functional status, and the patient satisfaction. There were many limitations in comparing outcomes across studies such as lack of proper randomization and/or allocation concealment, different populations, therapist bias, measurement differences etc. The findings of the RCTs suggest an improvement in symptoms of anxiety, worry, stress, depression, emotional stability, ego strength, feeling of security, and personality resulting in an improvement in quality of life and functional status in patients with generalized anxiety disorders. Since

the most discriminative somatic symptom of GAD compared to other anxiety disorders is muscle tension, muscle relaxation therapy (MRT) proved to be a valid treatment option for GAD patients, supported by four of our included studies except Conrad 2008.

Table 1. Strength of Evidence for Relaxation Therapy to Treat GAD

Outcome	Quantity and Type of Evidence	Intervention (n)/ Control (n)/Follow-up	Estimate of Effect	Study Limitations (Risk of Bias)	Inconsistency	Indirectness	Imprecision	Publication Bias	GRADE of Evidence for Outcome
Anxiety symptoms	5 RCTs (Dugas 2010; Hayes-Skelton, 2013; Janbozorgi, 2009; Hoyer, 2009; Conrad, 2008)	Total (n=64); CBT (n=33); AR (n=31) F/U: 6 mo., 12 mo., 24 mo.	**STAI-T** **Posttest** (n=64); Mean ± SD; CBT: 45.45±9.11; AR: 46.03±9.75 **Pretest-Posttest ES:** CBT 0.55; AR.36; WL 0.16 **Long-Term outcome:** the STAI-T slope, coefficient=−1.33, t (30) =−2.64, p<.05; **6 mos. F/U** (n=50); Mean ± SD; CBT: 43.30±9.68; AR: 45.52±9.10 **12 mos. F/U** (n=50) Mean ± SD; CBT: 41.38±8.79; AR: 43.16±8.39	Yes (-1)	No	No	Yes (-1); small sample size	No	Low

Outcome	Quantity and Type of Evidence	Intervention (n)/ Control (n)/Follow-up	Estimate of Effect	Study Limitations (Risk of Bias)	Inconsistency	Indirectness	Imprecision	Publication Bias	GRADE of Evidence for Outcome
			24 mos. F/U (n=42); Mean ± SD; CBT: 41.93±9.29; AR: 43.54±9.39; **Long-Term outcome**: the STAI-T slope, coefficient=−1. 33, t (30) =−2.64, p<.05; **CBT, and not AR would lead to continued improvement over 2 years following end of treatment at statistically significant levels**						
		Total = 81ABBT (n=40) vs. AR (n=41) 6 mos.	**SIGH-A** Time Estimate (-5.03); SE (0.70); **p <.001**; 95% CI [-6.44 to -3.63]; **anxiety symptoms significantly decreased across**	Yes (-1)	No	No	No	No	Moderate

Outcome	Quantity and Type of Evidence	Intervention (n)/ Control (n)/Follow-up	Estimate of Effect	Study Limitations (Risk of Bias)	Inconsistency	Indirectness	Imprecision	Publication Bias	GRADE of Evidence for Outcome
			treatment and follow-up; this change was similar across ABBT and AR **STAI** Time Estimate (-5.87); SE (0.91); **p <.001**; 95%CI [-7.68 to -4.05]; **anxiety symptoms significantly decreased across treatment and follow-up; this change was similar across ABBT and AR**						
		IRT (n=17) vs. Control (n=15) Post-test.	**STAI** State: IRT Mean ±SD: 31.87±8.53, **p<0.0001** vs. Control 52.32 ±10.57; **IRT was superior to control group at statistically significant** levels	Yes (-2)	No	No	Yes (-1); small sample size	No	Very low

Outcome	Quantity and Type of Evidence	Intervention (n)/ Control (n)/Follow-up	Estimate of Effect	Study Limitations (Risk of Bias)	Inconsistency	Indirectness	Imprecision	Publication Bias	GRADE of Evidence for Outcome
			Trait: IRT Mean±SD, 29.81 ±8.75, **p<0.0001** vs. 44.14 ±10.96; **IRT was superior to control group at statistically significant levels**						
		WL=29 AR[1]=28 WE[1]=29 F/U: 6 mo., 12 mo.	**STAI-T** **Posttest** WL: ref. AR: –6.72 (–10.6 to –2.8); p= **<0.01** WE: –6.50 (–10.0 to –2.9); **p<0.01**	Yes (-1)	No	No	No	No	Moderate
		AR or WLC (n=49); NAC (n=21) F/U: 6 wks.	**BAI** **Posttreatment** **AR:** N=17; M±SD: 11.59±12.11 **WLC**: N=15; M±SD: 12.13±6.86 **NAC**: N=18; M±SD: 1.22±1.93; **AR>WL** **Follow-up** **AR**: N=14; M±SD: 17±13.95	Yes (-1)	No	No	No	No	Moderate

Outcome	Quantity and Type of Evidence	Intervention (n)/ Control (n)/Follow-up	Estimate of Effect	Study Limitations (Risk of Bias)	Inconsistency	Indirectness	Imprecision	Publication Bias	GRADE of Evidence for Outcome
			NAC: N=19; M±SD: 2.05±3.49; **Self-Reported Posttreatment AR: N=17; M±SD: 3.71±2.05 WLC: N=15; M±SD: 5.53±2.1; NAC: N=18; M±SD: 1.39±1.94 - F(4,139.56)=2.99, P=.02 (significant); Favors AR> WLC Follow-up AR: N=14; M±SD: 4.93±2.2; NAC: N=19; M±SD: 0.95±1.47; Posttreatment to F/U F(1,16.89)=4.87, p=.04 (significant); worse anxiety at F/U**						

Outcome	Quantity and Type of Evidence	Intervention (n)/ Control (n)/Follow-up	Estimate of Effect	Study Limitations (Risk of Bias)	Inconsistency	Indirectness	Imprecision	Publication Bias	GRADE of Evidence for Outcome
Severity of GAD	3 RCTs (Dugas, 2010; Hayes-Skelton, 2013; Hoyer, 2009)	Total (n=64); CBT (n=33); AR (n=31) F/U: 6 mo., 12 mo., 24 mo.	**CSR Posttest;** Mean±SD: CBT: 1.73±2.23; AR: 2.55±2.55 **Pretest-Posttest ES** CBT 0.76; AR 0.62; and WL 0.39 **-Short-term outcome:** -CSR=24.67, p<0.001; **CBT was superior to WL at statistically significant levels** -CSR=8.27, p=0.006; **AR was superior to WL at statistically significant levels** **6 mo F/U** (n=50); Mean±SD; CBT: 1.33±1.86; AR: 1.43±1.88 **12 mo F/U** (n=50)	Yes (-1)	No	No	Yes (-1) small sample size	NA	Low

Outcome	Quantity and Type of Evidence	Intervention (n)/ Control (n)/Follow-up	Estimate of Effect	Study Limitations (Risk of Bias)	Inconsistency	Indirectness	Imprecision	Publication Bias	GRADE of Evidence for Outcome
			Mean±SD: CBT: 1.00 ±1.60; AR: 1.57 (1.91) **24 mo F/U** (n=42) Mean±SD; CBT: 1.21±1.75; AR: 1.21±2.08						
		Total =81; ABBT=40; AR=41 F/U: 6 mo.	**CSR** GAD Time Estimate (-1.41); SE (0.18); **p <.001**; 95%CI [-1.76 to -1.05]; severity of GAD decreased **significantly** across treatment and follow-up and that this change was similar across ABBT and AR	Yes (-1)	No	No	No	No	Moderate
		WL=29 AR[1]=28 WE[1]=29 F/U: 6 mo., 12 mo.	**HAMA comparison of posttest measures between groups** WL: ref. AR: –8.61 (–12.5 to –4.6); p= <0.01	Yes (-1)	No	No	No	No	Moderate

Outcome	Quantity and Type of Evidence	Intervention (n)/ Control (n)/Follow-up	Estimate of Effect	Study Limitations (Risk of Bias)	Inconsistency	Indirectness	Imprecision	Publication Bias	GRADE of Evidence for Outcome
			WE: –8.03 (–11.6 to –4.5); **p <0.01** **BSI-GSI** **Posttest** WL: ref. AR: –0.33 (–0.5 to –0.1); p <0.01 WE: –0.30 (–0.5 to –0.1); **p <0.01** **HAMD** **Posttest** WL: ref. AR: –5.74 (–8.3 to –3.1); p <0.01 WE: –5.82 (–8.2 to –3.4); p <0.01						
Pathological worry symptoms (PSWQ)	4 RCTs (Dugas 2010; Hayes-Skelton, 2013; Hoyer, 2009; Conrad, 2008)	Total (n=64); CBT (n=33); AR (n=31) F/U: 6 mo., 12 mo., 24 mo.	Posttest (n=65); (Mean [SD]): CBT: 51.13 (9.87); AR: 52.16 (8.04); WL: 58.80 (9.13); Posttest; Mean±SD: CBT: 50.79±10.24; AR: 51.21±7.90 Pretest-Posttest ES: CBT 0.74; AR 0.34; WL 0.03	Yes (-1)	No	No	Yes (-1)	No	Low

Outcome	Quantity and Type of Evidence	Intervention (n)/ Control (n)/Follow-up	Estimate of Effect	Study Limitations (Risk of Bias)	Inconsistency	Indirectness	Imprecision	Publication Bias	GRADE of Evidence for Outcome
			Short-term outcome: PSWQ=25.30, p<0.001; CBT was superior to WL at statistically significant levels -Long-term outcome: the PSWQ slope, coefficient = −1.98, t(30) = −3.99, p<.001; CBT, and not AR, would lead to continued progress over follow-up at statistically significant levels 6 mo F/U (n=50); Mean±SD: CBT: 48.70±10.33; AR: 49.09±7.49 12 mo F/U (n=50) Mean±SD: CBT:						

Outcome	Quantity and Type of Evidence	Intervention (n)/ Control (n)/Follow-up	Estimate of Effect	Study Limitations (Risk of Bias)	Inconsistency	Indirectness	Imprecision	Publication Bias	GRADE of Evidence for Outcome
			45.83±8.67; AR: 46.74±8.61 24 mo F/U (n=42) Mean ±SD: CBT: 45.30±8.01; AR: 48.17±11.72						
		Total =81; ABBT=40; AR=41 F/U: 6 mo.	Time Estimate (-8.94); SE (1.25); **p <.001**; 95%CI [-11.41 to -6.46]; **ABBT improved excessive worry and tension significantly over time, similar effect was seen across ABBT and AR**	Yes (-1)	No	No	No	No	Moderate
		WL=29 AR[1]=28 WE[1]=29 F/U: 6 mo., 12 mo.	**Posttest** WL: ref. AR: –7.54 (–11.6 to –3.4), p= <0.01 WE: –5.98 (–10.0 to –1.9); p <0.01	Yes (-1)	No	No	No	No	Moderate

Outcome	Quantity and Type of Evidence	Intervention (n)/ Control (n)/Follow-up	Estimate of Effect	Study Limitations (Risk of Bias)	Inconsistency	Indirectness	Imprecision	Publication Bias	GRADE of Evidence for Outcome
			6 mo F/U AR: MD= –0.13 (–2.4 to 2.2); p=0.91 (NS); **12 mo F/U** AR: MD= –1.25 (–4.0 to 1.5); p=0.36 (NS)	Yes (-1)	No	No	Yes (-1); wide 95% CI	No	Low
			6 mo F/U WE: MD= –3.48 (–6.6 to –0.3), p<0.05 Favors **WE>AR significantly**	Yes (-1)	No	No	No	No	Moderate
			12 mo F/U WE: MD=–3.14 (–6.2 to 0.1); p<0.05 Favors **WE>AR significantly**	Yes (-1)	No	No	Yes (-1)	No	Low
		AR or WLC (n=49); NAC (n=21) 6 wks. f/u	**<u>Posttreatment</u>** **AR:** N=17; M±SD: 53.29±12.83 **WLC**: N=15; M±SD: 59±10.45 **NAC:** N=18; M±SD: 27.61±8.68	Yes (-1)	No	No	No	No	Moderate

Outcome	Quantity and Type of Evidence	Intervention (n)/ Control (n)/Follow-up	Estimate of Effect	Study Limitations (Risk of Bias)	Inconsistency	Indirectness	Imprecision	Publication Bias	GRADE of Evidence for Outcome
			<u>Follow-up</u> **AR**: N=14; M±SD: 47.93±12.23 **NAC:** N=19; M±SD: 31.53±7.31 **Self-rated worry:** **<u>Posttreatment</u>** **AR:** N=17; M±SD: 3.41±2.67 **WLC:** N=15; M±SD: 5.73±2.02; **NAC:** N=18; M±SD: 1.11±2.27 F(4,137.03)=2.58, p=.04 (significant); ***Favors AR> WLC*** **<u>Follow-up</u>** **AR**: N=14; M±SD: 4.86± 2.93 **NAC:** N=19; M±SD: 1.00± 1.80; **<u>Posttreatment to F/U:</u>** p=.06						

Outcome	Quantity and Type of Evidence	Intervention (n)/ Control (n)/Follow-up	Estimate of Effect	Study Limitations (Risk of Bias)	Inconsistency	Indirectness	Imprecision	Publication Bias	GRADE of Evidence for Outcome
			(NS); worse worry at F/U						
Depressive symptoms	4 RCTs (Dugas, 2010; Hayes-Skelton, 2013; Hoyer, 2009; Conrad, 2008)	CBT (n=33); AR (n=31) F/U: 6 mo., 12 mo., 24 mo.	Pretest (n=64); Mean±SD; CBT: 13.67±7.91; AR: 51.07±9.08 Posttest (n=64); Mean±SD; CBT: 8.70± 6.89; AR: 9.71± 8.74; 6 mo F/U (n=50); Mean±SD; CBT: 7.81± 7.45; AR: 8.00± 6.90 12 mo F/U (n=50) Mean±SD; CBT: 6.52± 5.27; AR: 6.74± 7.83 24 mo F/U (n=42); Mean±SD; CBT: 6.81± 5.59; AR: 6.46±	Yes (-1)	No	No	Yes (-1)	No	Low

Outcome	Quantity and Type of Evidence	Intervention (n)/ Control (n)/Follow-up	Estimate of Effect	Study Limitations (Risk of Bias)	Inconsistency	Indirectness	Imprecision	Publication Bias	GRADE of Evidence for Outcome
			5.47						
		Total =81; ABBT=40; AR=41 F/U: 6 mo.	**DASS-Stress** Time Estimate (-6.84); SE (0.92); **p <.001**; 95% [-8.67 to -5.02]; **BDI-II** Time Estimate (-0.87); SE (0.15); **p <.001**; 95%CI [-1.18 to -0.56]; **Decrease in rate of depression symptoms and stress was statistically significant and similar in both ABBT and AR**	Yes (-1)	No	No	No	No	Moderate
		WL=29 AR[1]=28 WE[1]=29 F/U: 6 mos. ,12 mos.	**BDI** Posttest WL: ref. AR: –4.48 (–7.3 to –1.6); p <0.01	Yes (-1)	No	No	No	No	Moderate
			Posttest WE: –2.52 (–5.4 to 0.4); p= 0.09 (NS)	Yes (-1)	No	No	Yes (-1); wide 95% CI	No	Low

Outcome	Quantity and Type of Evidence	Intervention (n)/ Control (n)/Follow-up	Estimate of Effect	Study Limitations (Risk of Bias)	Inconsistency	Indirectness	Imprecision	Publication Bias	GRADE of Evidence for Outcome
		AR or WLC (n=49); NAC (n=21) 6 wks. f/u	**<u>Pretreatment</u>** **<u>AR:</u>** N=29; M±SD: 15.69±7.03 **WLC**: N=20; M±SD: 13.95±6.05 **NAC**: N=21; M±SD: 1.1±1.55 *No notable differences between AR and WLC* **<u>Posttreatment</u>** **AR:** N=17; M±SD: 11.59±7.37 **WLC:** N= 15; M±SD: 12.67±8.37 **NAC:** N= 18; M±SD: 0.83±1.69 **<u>Follow-up</u>** AR: N=14; M±SD: 12.5±6.25 NAC: N= 19; M±SD:1.42±2.01	Yes (-1)	No	No	No	No	Moderate

Outcome	Quantity and Type of Evidence	Intervention (n)/ Control (n)/Follow-up	Estimate of Effect	Study Limitations (Risk of Bias)	Inconsistency	Indirectness	Imprecision	Publication Bias	GRADE of Evidence for Outcome
Somatic symptoms	3 RCTs (Dugas 2010; Hoyer, 2009; Conrad, 2008)	Total (n=64); CBT (n=33); AR (n=31) F/U: 6 mo., 12 mo., 24 mo.	**WAQ-Som** **Posttest** (n=65); Mean ±SD: CBT: 17.74 ±4.45; AR: 17.91 ±4.81; WL: 21.45± 3.65; **Pretest-Posttest ES:** CBT 0.61; AR 0.37; WL 0.23 **-Short-term outcome:** WAQ Som=8.87, **p=0.005**; **CBT was superior to WL at statistically significant levels;** **6 mo F/U** (n=50); WAQ-Som Mean±SD; CBT: 15.63±4.12; AR: 18.22±4.78 **12 mo F/U** (n=50) WAQ-Som Mean±SD; CBT: 14.90±4.99;	Yes (-1)	No	No	Yes (-1); small sample size	No	Low

Outcome	Quantity and Type of Evidence	Intervention (n)/ Control (n)/Follow-up	Estimate of Effect	Study Limitations (Risk of Bias)	Inconsistency	Indirectness	Imprecision	Publication Bias	GRADE of Evidence for Outcome
			AR: 15.89±4.03; **24 mo F/U** (n=42); Mean±SD; CBT: 15.63±4.84; AR: 15.77±5.17						
		WL=29 AR[1]=28 WE[1]=29 F/U: 6 mo., 12 mo.	**HAMA Posttest** WL: ref. AR: –3.01 (–4.9 to –1.0); p= <0.01 WE: –3.08 (–5.2 to –0.9); p <0.01	Yes (-1)	No	No	No	No	Moderate
		AR or WLC (n=49); NAC (n=21) 6 wks. f/u	**<u>Pretreatment</u> AR:** N=29; M±SD: 19.72±5.68 **WLC:** N=20; M±SD: 18.8±5.53 **NAC:** N=21; M±SD: 8.71±2.19; **No notable differences between AR and WLC <u>Posttreatment</u> AR:** N= 17; M±SD: 16.35±3.98	Yes (-1)	No	No	No	No	Moderate

Outcome	Quantity and Type of Evidence	Intervention (n)/ Control (n)/Follow-up	Estimate of Effect	Study Limitations (Risk of Bias)	Inconsistency	Indirectness	Imprecision	Publication Bias	GRADE of Evidence for Outcome
			WLC: N= 13; M±SD: 18±6.78 **NAC: N**= 16**;** M±SD: 8.94±2.08 **Follow-up** **AR:** N**=** 14; M±SD: 17.93±6.49 **NAC:** 18; M±SD: 9.5±2.79						
Cognitive symptoms	2 RCTs (Conrad 2008, Hoyer 2009)	AR or WLC (n=49); NAC (n=21) F/U:6 week	**Pretreatment** **AR:** N=29; M±SD: 22.45±6.05 **WLC:** N=20; M±SD: 22.5±5.84 **NAC:** N=21; M±SD: 7.9±1.95; *No notable differences between AR and WLC* **Posttreatment** **AR:** N=17; M±SD: 18.47±6.92 WLC: N=13; M±SD: 21±6.04	Yes (-1)	No	No	No	No	Moderate

Outcome	Quantity and Type of Evidence	Intervention (n)/ Control (n)/Follow-up	Estimate of Effect	Study Limitations (Risk of Bias)	Inconsistency	Indirectness	Imprecision	Publication Bias	GRADE of Evidence for Outcome
			NAC: N=16; M±SD: 8.31±1.82 **<u>Follow-up</u>** **AR**: N=14; M±SD: 18.7±16.7 **NAC: N=18;** M±SD: 8.06±1.66						
Overall improvement in GAD	2 RCTs (Dugas 2010, (Hayes-Skelton, 2013)	Total (n=64); CBT (n=33); AR (n=31) F/U: 6 mo., 12 mo., 24 mo.	**CGI-I** **Pretest (n=64); Mean±SD: NA** **Posttest (n=64); Mean±SD;** **CBT: 2.24±0.90; AR: 2.84±1.04;** **Short-term outcome: CGI-I=13.87, p=0.001; CBT was superior to WL at significant levels** **Long-Term outcomes: CGI-I slope, coefficient=−.14, t(30)=−2.28, p<0.05; CBT, and not AR would lead to continued progress over**	Yes (-1)	No	No	Yes (-1); small sample size	No	Low

Outcome	Quantity and Type of Evidence	Intervention (n)/ Control (n)/Follow-up	Estimate of Effect	Study Limitations (Risk of Bias)	Inconsistency	Indirectness	Imprecision	Publication Bias	GRADE of Evidence for Outcome
			follow-up at statistically significant levels **6 mo F/U (n=50); Mean±SD;** **CBT: 1.96±0.76; AR: 2.04±1.11** **12 mo F/U (n=50) Mean±SD;** **CBT: 1.69 ±0.97; AR: 2.10 ±0.83** **24 mo F/U (n=42); Mean±SD;** **CBT: 1.75±0.84; AR: 1.93±1.21** **CBT was superior to WL at statistically significant levels;** **Long-Term outcomes: CGI-I slope, coefficient=−.14, t(30)=−2.28, p<0.05; Long-Term outcomes: CGI-I slope, coefficient=−.14,**						

Outcome	Quantity and Type of Evidence	Intervention (n)/ Control (n)/Follow-up	Estimate of Effect	Study Limitations (Risk of Bias)	Inconsistency	Indirectness	Imprecision	Publication Bias	GRADE of Evidence for Outcome
			t(30)=−2.28, p<0.05; CBT, and not AR, would lead to continued progress over follow-up at statistically significant levels Posttest (n=65); Mean ±SD: CBT:2.35±0.94; AR: 2.77± 1.02; WL: 3.35±0.81 CGI-I=13.87, p=0.001; **CBT was superior to WL at significant levels** **Long-Term outcomes:** CGI-I slope, coefficient=−.14, t (30) =−2.28, p<0.05 at significant levels **Remission rates in CBT**: 70% at posttreatment, 76% at 6-month follow-up, 84% at 12-month follow-up, and						

Outcome	Quantity and Type of Evidence	Intervention (n)/ Control (n)/Follow-up	Estimate of Effect	Study Limitations (Risk of Bias)	Inconsistency	Indirectness	Imprecision	Publication Bias	GRADE of Evidence for Outcome
			77% at 24-month follow-up. **Remission rates in AR:** 55% at posttreatment, 70% at 6-month follow-up, 68% at 12-month follow-up, and 61% at 24-month follow-up. **Medication use in CBT group:** percentages of participants taking anxiolytic or antidepressant medication were 58% at pretreatment, 52% at posttreatment, 46% at 6-month follow-up, 45% at 12-month follow-up, and 36% at 24-month follow-up. In the AR condition, percentages were 58% at pretreatment, 50% at posttreatment, 57% at 6-month						

Outcome	Quantity and Type of Evidence	Intervention (n)/ Control (n)/Follow-up	Estimate of Effect	Study Limitations (Risk of Bias)	Inconsistency	Indirectness	Imprecision	Publication Bias	GRADE of Evidence for Outcome
			follow-up, 67% at 12-month follow-up, and 46% at 24-month follow-up. **Use of medication was not significantly different in both treatments**						
		Total =81; ABBT=40; AR=41 F/U: 6 mo.	GAD Time Estimate (-1.41); SE (0.18); **p <.001**; 95%CI [-1.76 to -1.05]; severity of GAD decreased **significantly** across treatment and follow-up and that this change was similar across ABBT and AR	Yes (-1)	No	No	No	No	Moderate

Outcome	Quantity and Type of Evidence	Intervention (n)/ Control (n)/Follow-up	Estimate of Effect	Study Limitations (Risk of Bias)	Inconsistency	Indirectness	Imprecision	Publication Bias	GRADE of Evidence for Outcome
Quality of life	1 RCT (Hayes-Skelton, 2013)	Total =81; ABBT=40; AR=41 F/U: 6 mo.	**QOLI** Time Estimate (0.50); SE (0.12); **p <.001**; 95%CI [0.26 to 0.75]; **rate of improvement in Quality of Life (QoL) for degree of importance and level of satisfaction over time was statistically significant and similar in ABBT and AR**	Yes (-1)	No	No	No	No	Moderate

Outcome	Quantity and Type of Evidence	Intervention (n)/ Control (n)/Follow-up	Estimate of Effect	Study Limitations (Risk of Bias)	Inconsistency	Indirectness	Imprecision	Publication Bias	GRADE of Evidence for Outcome
Quality of life (Personality Factor C) Emotionally less stable, reactive vs emotionally stable	1 RCT (Janbozorgi 2009)	IRT (n=17) vs. control (n=15) F/U: NR	Posttest-Pretest IRT Mean±SD, 4.12±5.81 vs. Control -0.40±3.62; p=0.014; IRT was superior to control group at statistically significant levels	Yes (-2)	No	No	Yes (-1)	No	Very low
Quality of life (Personality Factor H) Shy vs venturesome	1 RCT (Janbozorgi 2009)	IRT (n=17) vs. control (n=15) F/U: NR	Posttest-Pretest IRT Mean±SD, 4.78±6.10 vs. Control –0.40± 3.40; p=0.006; IRT was superior to control group at statistically significant levels	Yes (-2)	No	No	Yes (-1)	No	Very low

Outcome	Quantity and Type of Evidence	Intervention (n)/ Control (n)/Follow-up	Estimate of Effect	Study Limitations (Risk of Bias)	Inconsistency	Indirectness	Imprecision	Publication Bias	GRADE of Evidence for Outcome
Quality of life (Personality Factor O) Self-assured vs apprehensive	1 RCT (Janbozorgi 2009)	IRT (n=17) vs. control (n=15) F/U: NR	Posttest-Pretest IRT Mean±SD, -4.72±4.39 vs. Control –0.27± 3.97; p=0.005; IRT was superior to control group at statistically significant levels	Yes (-2)	No	No	Yes (-1)	No	Very low
Quality of life (Personality Factor Q4) Relaxed vs tense	1 RCT (Janbozorgi 2009)	IRT (n=17) vs. control (n=15) F/U: NR	Posttest-Pretest IRT Mean±SD, -6.56± 7.95 vs. Control 0.80±4.20; p=0.003; IRT was superior to control group at statistically significant levels	Yes (-2)	No	No	Yes (-1)	No	Very low
Patient Satisfaction	1 RCTs (Hayes-Skelton 2013)	Total =81; ABBT=40; AR=41 F/U: 6 mos.	Posttreatment ABBT: 7.39±1.41, AR:7.41± 1.66; **rate of improvement in satisfaction over time was statistically**	Yes (-1)	No	No	No	No	Moderate

Outcome	Quantity and Type of Evidence	Intervention (n)/ Control (n)/Follow-up	Estimate of Effect	Study Limitations (Risk of Bias)	Inconsistency	Indirectness	Imprecision	Publication Bias	GRADE of Evidence for Outcome
			significant and similar in ABBT and AR						
Functional status Responder status	2 RCTs (Hayes-Skelton 2013, Hoyer 2009)	Total =81; ABBT=40; AR=41 F/U: 6 mo.	**Posttreatment 63.3–80.0% in ABBT and 60.6–78.8% in AR exhibited clinically significant change.** **Follow-up (6 months) 66.7–80.0% in ABBT and AR (60.6–78.8%), exhibited clinically significant change.** No significant differences between conditions at either time point, with small effect sizes (ds from 0.01 to 0.28).	Yes (-1)	No	No	No	No	Moderate

Outcome	Quantity and Type of Evidence	Intervention (n)/ Control (n)/Follow-up	Estimate of Effect	Study Limitations (Risk of Bias)	Inconsistency	Indirectness	Imprecision	Publication Bias	GRADE of Evidence for Outcome
		WL=29 AR[1]=28 WE[1]=29 F/U: 6 mo. ,12 mo	**HAMA Posttest** WE [n = 15 (48%)] vs. AR [n = 15 (56%)]; reached full end-state functioning. with HAMA score of 10 or less; **Treatment Response: Posttest** WE [n = 13 (45%); vs. AR [n = 14 (47%); 50% reduction in both active groups in HAMA scores	Yes (-1)	No	No	No	No	Moderate

*Dugas 2010, short-term treatment refers to posttest; long-term outcome are follow-up at 6-,12,24 months. *Expert ratings for anxiety symptoms (HAMA) were not conducted at follow-up. [1] For between-group comparisons WL is used as reference group. [2] With control for prelevels GAD _ generalized anxiety disorder; *SE* _ standard error; *df* _ degrees of freedom; CI _ confidence interval; Severity Rating (CSR); pathological worry by Penn State Worry Questionnaire (PSWQ); Worry and Anxiety Questionnaire, somatic symptoms by Somatic subscale (WAQ-Som); anxiety by State-Trait Anxiety Inventory Trait version (STAI-T); depressive symptoms by Beck Depression Inventory II (BDI-II); global clinical improvement by Clinical Global Impression, Improvement subscale (CGI-I).;SIGH-A _ Structured Interview Guide for the Hamilton Anxiety Rating Scale; DASS _ Depression Anxiety Stress Scale; QOLI _ Quality of Life Inventory; Hamilton Anxiety Rating Scale (HAMA): measures overall severity of anxiety; HAMA somatic and HAMA psychic subscales of HAMA: measures somatic and psychic symptoms; The Global Severity Index (GSI) of the Brief Symptom Inventory (BSI) was used to assess general psychopathology; Hamilton Depression Scale (HAMD) measures the overall severity of anxiety and depressive symptoms

Table 2. GRADE Factors Used to Assess the Quality of a Body of Evidence

Evidence Category	Definition
Study Quality (Internal Validity or Risk of Bias)	Study quality considers the overall risk of bias rating of all the studies included in the evidence base. In this review, the overall risk of bias would be the average or median USPSTF rating for studies comprising an evidence base for a key outcome.
Consistency of Evidence	Consistency of evidence refers to the degree of similarity in the direction of effects or the degree of similarity in the effect sizes (magnitude of effect) across individual studies within an evidence base.
Directness of Evidence	Direct evidence directly compares interventions of interest in populations of interest and measures patient-oriented outcomes. Evidence can be indirect if the tested intervention differs from the intervention of interest, the study population differs from the population of interest, the outcomes differ from those of primary interest, or treatment comparisons have not been tested in head-to-head comparisons.
Precision of Evidence	Precision is the degree of certainty surrounding an estimate of effect with respect to an outcome. Precision is primarily assessed by examining the 95% confidence intervals around the summary effect size.

Link to GRADE Handbook: **http://gdt.guidelinedevelopment.org/app/handbook**

Table 3. Evidence Table for RCTs on Relaxation Therapy to Treat GAD

Study Details	Study Population	Treatment	Results	Conclusion/Limitations
Reference: Dugas et al. 2010 **Purpose:** To compare the CBT protocol to AR in terms of its short- and long-term benefits and to replicate the superiority of both treatments to a wait-list control condition. **Setting:** Anxiety Disorders Clinic of the Hôspital du Sacré-Coeur de Montréal and through referrals from general practitioners and mental health specialists in the Montreal area. Concordia University, Montreal **F/u:** 6-, 12-, and 24-months **Funding source:** **G**rant MOP-42454 from the Canadian Institutes of Health Research awarded to Michel J. Dugas	**Number of patients:** 65; n=23 CBT; n=22 AR; n=20 WL **Inclusion criteria:** 18 and 64 years of age, primary diagnosis of GAD with a Clinician's Severity Rating of at least 4/8 (moderate severity), a difference of at least 2 points on the Clinician's Severity Rating between GAD and all comorbid conditions; no change in medication type or dose during 4 to 12 weeks before assessment (4 weeks for benzodiazepines, 12 weeks for antidepressants and hypnotics); willingness to keep medication stable during the treatment phase of the study, no evidence of suicidal intent, no evidence of current substance abuse and no evidence of current or past schizophrenia, bipolar disorder, or organic mental disorder. **Exclusion criteria:** GAD was not the primary diagnosis, the severity of a comorbid disorder was not at least 2 points less on the Clinician's Severity Rating, or a medical problem	**Intervention: CBT—Cognitive-behavioral therapy** consisted of 12 weekly 1-hour sessions and covered the following treatment phases. 1. Psychoeducation and worry awareness training (1 session). 2. Uncertainty recognition and behavioral exposure (3 sessions). 3. Reevaluation of the usefulness of worry (1 session). 4. Problem-solving training (3 sessions). 5. Imaginal exposure (3 sessions). **AR—Applied relaxation** also consisted of 12 weekly 1-hour therapy sessions covering the following treatment phases. 1. Psychoeducation and tension awareness training (1 session). 2.Tension-release training (4 sessions). 3. Relaxation by recall (2 sessions). 4. Relaxation by counting (1 session).	**Overall severity of GAD (CSR);** **Pretest** (n=65); Mean ±SD: CBT: 5.78 ±1. 04; AR: 5.36 ±1.26; WL: 5.90 ±1.25, **Posttest (**n=65); ± Mean ±SD: CBT: 1.61 ±2.21; AR: 2.55 ±2.58; WL: 4.78 ±2.07; **ES:** CBT 0.76; AR 0.62; and WL 0.39 **-Short-term outcome:** -CSR=24.67, p<0.001; **CBT was superior to WL** -CSR=8.27, p=0.006; **AR was superior to WL** **Pathological worry (PSWQ)** **Pretest** (n=65); Mean ±S D: CBT: 61.65±8.27; AR: 58.01 ±5.51; WL: 57.34 ±9.78, **Posttest** (n=65); Mean ±SD: CBT: 51.13 ±9.87; AR: 52.16 ±8.04; WL: 58.80 ±9.13; **ES:** CBT 0.74; AR 0.34; WL 0.03 **-Short-term outcome:** PSWQ=25.30, p<0.001; **CBT was superior to WL at statistically significant levels** **-Long-term outcome**: the PSWQ slope, coefficient = −1.98, t (30) = −3.99, p<.001; **Somatic symptoms (WAQ-Som)** **Pretest** (n=65); Mean ±SD: CBT: 21.13±4.07); AR: 20.82 ±5.48; WL: 22.42±3.17 **Posttest** (n=65); Mean ±SD: CBT: 17.74 ±4.45; AR: 17.91 ±4.81; WL: 21.45± 3.65; **ES:** CBT 0.61; AR 0.37; WL 0.23	**Conclusion:** CBT and AR are efficacious treatments for GAD. At posttest, CBT was clearly superior to WL, AR was marginally superior to WL, and CBT was marginally superior to AR. CBT was superior to WL on 4 of 6 short-term outcomes, namely overall severity of GAD, pathological worry, somatic symptoms of GAD, and global clinical improvement. AR was superior to WL on only one short-term outcome, namely overall severity of GAD. Although both CBT and AR produce similar short- and long-term outcomes, and are equivalent at follow-up, only CBT appears to lead to continued improvement in worry, anxiety, and clinical improvement over the 2 years following the end of treatment for CBT participants. **Limitations:** Small sample size, allegiance effects, therapist bias, and reliability of the diagnoses. **Study ROB:** Some concerns due primarily to no blinding of patients, clinicians, and outcome assessors.

Study Details	Study Population	Treatment	Results	Conclusion/Limitations
	required immediate attention **Pt. baseline characteristics:** The mean age of the participants was 38.5 years (SD=12.0), 66.15% women, and an average of 15.3 years of education (SD=3.4). The ethnic composition of the sample was 91% White/European, 5% Middle Eastern, 2% Hispanic, and 2% Asian. In addition, 62.5% of participants were employed, 10.9% were students, and 26.6% were unemployed. The mean duration of GAD was 13.9 years (SD=16.7), Comorbid conditions were diagnosed in 58.5% of the sample, 55.4% of participants were taking anxiolytic or antidepressant medication and 43.1% had previously received CBT for an anxiety or mood disorder	5. Conditioned relaxation (3 sessions): **Wait-list Control (WL)** The duration of the WL condition was 12 weeks. Wait-listed participants were contacted by telephone every three weeks by the psychiatrist who had administered the MINI to monitor their state. **Outcomes of Interest:** overall severity of GAD by Clinician's Severity Rating (CSR); pathological worry by Penn State Worry Questionnaire (PSWQ); Worry and Anxiety Questionnaire, somatic symptoms by Somatic subscale (WAQ-Som); anxiety by State-Trait Anxiety Inventory Trait version (STAI-T); depressive symptoms by Beck Depression Inventory II (BDI-II); global clinical improvement by Clinical Global Impression, Improvement subscale (CGI-I)	-**Short-term outcome:** WAQ Som=8.87, p=0.005; **CBT was superior to WL at statistically significant levels** **Anxiety (STAI-T)** **Pretest** (n=65); Mean ±SD: CBT: 53.04±7.30; AR: 52.23 ±7.15; WL: 52.06±9.62 **Posttest** (n=65); Mean ±SD: CBT: 46.35±7.99; AR: 46.95 ±8.42; WL: 48.98±8.68; **ES:** CBT 0.55; AR.36; WL 0.16 **Long-Term outcome**: the STAI-T slope, coefficient=−1.33, t (30) =−2.64, p<.05; **Depression (BDI-II)** **Pretest** (n=65); Mean ±SD: CBT: 15.36±8.20; AR: 16.65 ±9.27; WL: 13.70±7.72 **Posttest** (n=65); Mean ±SD: CBT: 8.83±6.63; AR: 10.27±8.99; WL: 11.20± 7.26; **ES:** CBT 0.55; AR 0.49; WL 0.10 **Global clinical improvement (CGI-I)** Pretest: NA Posttest (n=65); Mean ±SD: CBT:2.35±0.94; AR: 2.77± 1.02; WL: 3.35±0.81 CGI-I=13.87, p=0.001; **CBT was superior to WL at significant levels** **Long-Term outcomes:** CGI-I slope, coefficient=−.14, t (30) =−2.28, p<0.05 at significant levels; continued improvement over the 2 years following end of treatment **Remission rates in CBT**: 70% at posttreatment, 76% at 6-month follow-up,	**Author conflict:** None reported.

Study Details	Study Population	Treatment	Results	Conclusion/Limitations
			84% at 12-month follow-up, and 77% at 24-month follow-up. **Remission rates in AR:** 55% at posttreatment, 70% at 6-month follow-up, 68% at 12-month follow-up, and 61% at 24-month follow-up. **Medication use in CBT group:** percentages of participants taking anxiolytic or antidepressant medication were 58% at pretreatment, 52% at posttreatment, 46% at 6-month follow-up, 45% at 12-month follow-up, and 36% at 24-month follow-up. In the AR condition, percentages were 58% at pretreatment, 50% at posttreatment, 57% at 6-month follow-up, 67% at 12-month follow-up, and 46% at 24-month follow-up. **Use of medication was unaffected by each of the treatments**.	
Reference: Janbozorgi et al., 2009 **Purpose:** To explore the effects of progressive relaxation training combined with lifestyle modification and spiritual training and determine their integrated effects on the anxiety factors of personality and emotional stability. **Setting:** University of Medical Science, Tehran (Iran);	**Number of patients:** Total (n=32); IRT (n=17); Control (n=15) **Inclusion criteria:** Women aged 18-39 years; diagnosed with GAD according to DSM-IV **Exclusion criteria:** Age <19y or >35y, principal diagnosis other than GAD, patients undergoing concurrent psychological treatment for anxiety disorder, had a current diagnosis of schizophrenia, an intellectual disability, or an organic mental disorder	**Intervention:** The IRT program is a structured program attended by participants in groups of 10–15 persons. Participants completed the 16PF questionnaire to measure 16 personality factors and were given a weekly task. The study group received 12 weekly group sessions of IRT, a lifestyle relaxation program and spiritual exercises. Each session lasted for about 1.5–2 hours and was divided into 4 sections: review of homework, relaxation training, discussion of	**Personality Factors**; (IRT; Control) Mean Difference (Mean±SD) **Emotional stability:** IRT 4.12±5.81 vs. Control -0.40±3.62; p=0.014 **Venturesome:** IRT 4.78±6.10 vs. Control –0.40± 3.40; p=0.006 **Apprehensive:** IRT Mean±SD, -4.72±4.39 vs. Control –0.27± 3.97; p=0.005 **Tense:** IRT Mean±SD, -6.56± 7.95 vs. Control 0.80±4.20**;** p=0.003 **State anxiety:** IRT Mean ±SD: 31.87±8.53, p<0.0001 vs. Control 52.32 ±10.57 **Trial anxiety:** IRT Mean±SD, 29.81 ±8.75, p<0.0001 vs. 44.14 ±10.96 **IRT was superior to control on all outcomes at statistically significant levels**	**Conclusion:** Emotional instability and level of anxiety were significantly reduced in the study group, there was a marked increase in scores for emotionally stability, relaxation, venturesome and a decrease in scores for apprehensive and fear. The STAI score was statistically significantly lower in the study group. Thus, IRT is an effective intervention to reduce anxiety, improve emotional stability, ego strength, feeling of security, and personality. **Emotional stability by itself results in success and**

Study Details	Study Population	Treatment	Results	Conclusion/Limitations
participants were referred to a counselling and psychotherapy center from both government and private Organizations, as well as self-referrals. **F/u:** NR **Funding source:** Thalieh Counselling Centre in Tehran	**Pt. baseline characteristics:** The mean age of the participants was 24.64±3.77 years; 35% were married and 87.5% were women.	lifestyle and spiritual dimensions. **Control:** The control group completed the pre-test 16PF questionnaires but did not take part in the interventions **Outcomes of Interest:** Factor C: Emotionally less stable, reactive vs. emotionally stable, Factor H: Shy vs. venturesome, Factor O: Self-assured vs. apprehensive, Factor Q4: Relaxed vs. tense, State anxiety, and Trait anxiety		**happiness which improves quality of life, functional status, and patient satisfaction** **Limitations:** Small sample size, selection bias, the nature of the interventions and confounding effect **Study RoB:** High; unclear randomization procedures; lack of blinding of patients, clinicians and outcome assessors, and self-reported outcomes. **Author conflict:** Thalieh Counselling Centre in Tehran for financing this research, participants referred to this center were selected for the study
Reference: Hayes-Skelton et al., 2013 **Purpose:** To examine whether an empirically and theoretically derived treatment combining mindfulness- and acceptance-based strategies with behavioral approaches (ABBT) would improve outcomes in generalized anxiety disorder (GAD) over an empirically	**Number of patients:** Randomized =81(n=1 didn't attend any sessions); Completers=63, Analyzed=82; ABBT=41; AR=41 **Inclusion criteria:** Principal diagnosis of GAD on the ADIS-IV with at least moderate severity on the clinician severity rating; reported a GAD onset that preceded their first episode of major depressive disorder; were stable on any medications for 3 months and were willing to	**Interventions:** **Acceptance-based behavior therapy (ABBT):** Elements of ABBT are mindfulness, acceptance, and valued action. Each session begins with a mindfulness exercise and a review of between session assignments, followed by the session-specific content and ends with the assignment of between-session activities. **Applied relaxation (AR):** focus is on relaxation skills primarily through	**<u>Primary outcomes</u>** Pretreatment (N=81); Posttreatment (N=63); 6-month F/U (N=55) **Severity of anxiety (CSR)** **ABBT (M ±SD):** Pretreatment, 5.53 ±0.55; Posttreatment, 3.03 ±1.38; 6-month follow-up, 2.88 ±1.59; **AR (M ±SD):** Pretreatment, 5.44 ±0.71; Posttreatment, 2.70 ±1.57; 6-month follow-up, 2.77 ±1.59; No pretreatment differences on any outcome variables: GAD severity, F (1, 79) = 0.37, ***p*= .54 (NS)** **SIGH-A** **ABBT (M ±SD):** Pretreatment, 19.31 ±6.55; Posttreatment, 10.98 ±7.06; 6-month follow-up, 9.54 ±7.53;	**Conclusion:** Both an acceptance-based behavior therapy and applied relaxation led to statistically and clinically significant change across treatment and short-term follow-up. Between 63.3 and 80.0% of participants in ABBT and 60.6 and 78.8% in AR experienced clinically significant change at posttreatment and follow-up. Patients in ABBT and AR gained large significant effects for change at post treatment and 6 months in all

Study Details	Study Population	Treatment	Results	Conclusion/Limitations
supported treatment (AR). **Setting:** University of Massachusetts Boston **F/u:** 6 months **Funding source:** National Institute of Mental Health Grants MH074589	maintain current psychotropic medication levels and to refrain from other psychosocial treatments for anxiety or mood problems during the course of therapy; were fluent in English; and were 18 years or older. **Exclusion criteria:** diagnoses of comorbid bipolar disorder, a psychotic disorder, an autism-spectrum disorder, or current substance dependence. **Pt. baseline characteristics:** 65.4% female, 80.2% identified as White, average age 32.92. Previous psychotherapy ABBT 85%; AR 85.4%, Previous CBT/skills-based therapy: ABBT 22.5%, AR 22%, Taking psychotropic medication: ABBT 22.5%; AR 34.1%, Additional diagnoses ABBT 62.5%; AR 75.6%	diaphragmatic breathing and progressive muscle relaxation; enhancing awareness of early signs of anxiety; and finally applying a brief relaxation exercise in response to early signs of anxiety. Both treatments were 16 sessions in length, with four initial weekly 90-min sessions followed by weekly 60-min sessions and a biweekly taper between Sessions 14, 15, and 16. **Outcomes of Interest:** **Primary outcomes:** GAD (CSR) = clinician severity rating, SIGH-A=Structured Interview Guide for the Hamilton Anxiety Rating Scale, PSWQ =Penn State Worry Questionnaire for excessive worry; DASS=Depression Anxiety Stress Scale, and the STAI=State–Trait Anxiety Inventory for anxiety. **Secondary outcomes:** Beck Depression Inventory—II, Quality of Life Inventory, and number of comorbid diagnoses.	**AR (M ±SD):** Pretreatment, 20.54 ±6.79; Posttreatment, 11.48 ±6.20; 6-month follow-up, 10.75 ±6.93; No pretreatment differences on any outcome variables: SIGH-A, $F(1, 79)=0.69$, ***p*=.41 (NS)** **PSWQ** **ABBT (M ±SD):** Pretreatment, 67.67 ±8.10; Posttreatment, 51.03 ±8.46; 6-month follow-up, 50.93 ±10.72; **AR (M ±SD):** Pretreatment, 70.41 ±6.22; Posttreatment, 52.28 ±10.69; 6-month follow-up, 53.16 ±9.93; No pretreatment differences on any outcome variables: PSWQ, $F(1, 77)=2.86$, ***p*= .10 (NS)** **DASS-Stress** **ABBT (M ±SD):** Pretreatment, 24.49 ±8.73; Posttreatment, 13.37 ±6.44; 6-month follow-up, 12.84 ±7.68; **AR (M ±SD):** Pretreatment, 24.58 ±7.64; Posttreatment, 12.00 ±8.43; 6-month follow-up, 11.53 ±7.75; No pretreatment differences on any outcome variables DASS-Stress, $F(1, 77)=0.002$, ***p*= .96 (NS)** **STAI** **ABBT (M ±SD):** Pretreatment, 53.94 ±9.81; Posttreatment, 43.46 ±10.39; 6-month follow-up, 42.88 ±10.94; **AR (M ±SD):** Pretreatment, 53.30 ±7.87; Posttreatment, 43.48 ±12.07; 6-month follow-up, 40.72 ±10.44; No pretreatment differences on any outcome variables, STAI, $F(1, 77) = 0.10$, ***p* = .75 (NS)** **<u>Secondary outcome</u>** **BDI–II**	the primary outcome measures. Overall, patients in ABBT and AR maintained gains across all outcome measures at post treatment and 6 months but was not significant. All effect sizes were small, indicating comparable maintenance The treatments are comparably credible and acceptable to participants. ABBT is a viable alternative for treating GAD. **There are no significant differences between the two treatments, ABBT and AR, *F* (1, 62) =0.003, *d* =0.01, *<u>p</u>* =.96 (NS).** **Limitations:** Therapist bias, allegiance, reliability of the diagnoses; poor external validity **Study ROB**: Some concerns **Author conflict:** None reported

Study Details	Study Population	Treatment	Results	Conclusion/Limitations
			ABBT (M ±SD): Pretreatment, 19.33 ±11.10; Posttreatment, 9.54 ±10.76; 6-month follow-up, 8.93 ±11.91; AR Pretreatment, 17.92 ±10.60; Posttreatment, 7.85 ±8.51; 6-month follow-up, 7.47 ±8.73; No pretreatment differences on any outcome variables, $F(1, 77)= 0.31$, ***p* = .58 (NS)** **QOLI±±** **ABBT (M ±SD):** Pretreatment, 0.24 ±2.14; Posttreatment, 1.56 ±1.78; 6-month follow-up, 1.41 ±1.80; **AR (M ±SD):** Pretreatment, 0.86 ±1.18; Posttreatment, 1.87 ±1.60; 6-month follow-up, 1.92 ±1.41; No pretreatment differences on any outcome variables $F (1, 77) =2.58$, ***p* =.11 (NS)** **No. additional diagnoses** **ABBT (M ±SD):** Pretreatment, 0.95 ±0.98; Posttreatment, 0.55 ±0.92; 6-month follow-up, 0.48 ±0.92; **AR (M ±SD):** Pretreatment, 1.15 ±0.85; Posttreatment, 0.52 ±0.71; 6-month follow-up, 0.37 ±0.56 **Responder Status (3 of 4)** (N=63) **Posttreatment** ABBT: 70.0% (21/30); AR: 78.8% (26/33); **p=0 .42 (NS)** **6-month** ABBT: 76.0% (19/25); AR: 71.4% (20/28); **p=0 .71 (NS)** ABBT:70.0% (21/30); AR= 72.7% (24/33); **p=0 .81 (NS)** **High End-State Functioning (3 of 4)** **Posttreatment**	

Study Details	Study Population	Treatment	Results	Conclusion/Limitations
			ABBT: 63.3% (19/30); AR: 60.6% (20/33); **p= 0.82 (NS)** **6-month** 80.0% (20/25) 67.8% (19/28), **p= 0.32 (NS);** 0.28; 73.3% (22/30) 60.6% (20/33); **p=0.28 (NS)**	
Reference: Hoyer et al., 2009 **Purpose:** To examine whether Worry exposure (WE) alone is as efficacious as the empirically supported stand-alone treatment applied relaxation (AR) for GAD **Setting:** Outpatient psychotherapy unit of the Technische Universität Dresden, Germany **F/u:** 6 months, 12 months **Funding source:** This study was funded by the German Research Council (DFG; HO, 1900/1-3).	**Number of patients:** Total =73; 1st Randomization: AR=18; WE=24; WL=31; 2nd Randomization for WL patients: AR=32; WE=36 **Inclusion criteria:** Primary DSM-IV diagnosis of GAD; age between 18 and 70 years and antidepressant drugs begun before and maintained on a stable dosage throughout the study **Exclusion criteria:** Serious physical, impairment, any lifetime history of schizophrenia, bipolar disorder, seizure or organic brain syndrome, substance abuse or dependence within the past year, serious personality disorder, any concurrent psychotherapeutic intervention or benzodiazepine use. **Pt. baseline characteristics:** The majority of the participants were female (n = 52; 71%). The mean age was 45.4	**Intervention**: The treatment was manualized 15 weekly sessions with AR or WE **Applied Relaxation (AR):** commenced with psychoeducation. Beginning with progressive muscle relaxation, the patients were trained in different steps of relaxation procedures during the subsequent 6–7 sessions. They were also taught to identify early signs of tension and anxiety. In the final stage of therapy, application of rapid relaxation following the recognition of the first signs of anxiety, as provoked by imagining feared situations, was practiced in the session. The patients then applied their relaxation skills whenever signals of tension, worrying or anxiety occurred in daily life. There was no explicit confrontation instruction, although transfer to everyday situations was encouraged at the end of treatment (sessions 14 and 15)	**Applied relaxation** **HAMA**: - n=28; 22.71±7.35 (before); 12.21±8.82 (after); MD: –10.50; CI (14.0 to –7.0); p=<0.01; **HAMA somatic**: - n=28; 9.86±3.96 (before); 5.64±4.24 (after); MD: –4.23 (–6.1 to –2.4); p= <0.01; **HAMA psychic:** **-** n= 28; 12.83±4.38 (before); 6.67±5.00 (after); MD: –6.16 (–8.1 to –4.2); p= <0.01; **STAI-T**: n=26; 51.69 ±5.08 (before);45.04±8.71 (after); MD=–6.65 (–9.7 to –3.6), p= <0.01; **PSWQ**: - n= 28; 56.84± 8.15 (before); 49.55 ±9.49 (after); MD= –0.79 (–10.5 to –4.0); p=<0.01; -n=27; 49.22±8.10 (FU 6 mo); -n=26; 48.38±8.56 (FU 12 mo) **MCQ II**: - n=28; 43.46±7.98 (before); 36.49±9.27 (after); MD= –6.97 (–9.8 to –4.1); p= <0.01; - n=27; 35.78±7.52(FU 6 mo); n=27; 34.22±8.67 (FU 12 mo) **WBSI:** - n=28; 47.7±9.86 (before); 39.36±11.47 (after); MD= –8.34 (–12.1 to –4.5); p <0.01; - n=27; 39.52±11.52 (FU 6 mo); n=27; 38.27±11.64 (FU 12 mo) **BSI-GSI:** -n=28; 0.81±0.44 (before); 0.51±0.46 (after); - n=26; 0.51±0.44 (FU 6 mo); n=27; 0.51±0.44 (FU 12 mo)	**Conclusion** WE as a stand-alone treatment for GAD is as efficacious as AR with no significant difference at either the 6- or 12-month follow-up. Both active treatments (WE, AR) were more efficacious than the WL. Specifically, the WE improved significantly relative to AR treatment on measures of worry frequency (PSWQ) and salient cognitive variables (WBSI; as a statistical trend: MCQ II). At the 12-month follow-up, improvements noted in the WE condition were maintained at a significant level. AR group improved significantly in 1 of the 2 salient cognitive variables (i.e. MCQ II). These results suggest that the treatment effects improved or were maintained in the year following treatment for both groups. The pre-/posttreatment effects were high for HAMA (SMD >1); and for STAI (SMD>0.87) **Limitations:**

Study Details	Study Population	Treatment	Results	Conclusion/Limitations
	±12.48 years. The sample had an average level of education: most of the participants reported completing a 10th-grade education (n = 35, 48%), approximately a third at least a 12th-grade education (n = 27; 37%) and less than a fifth an 8th-grade education (n = 11; 15%). Most participants were married (n = 52, 71%), while 13 (17%) were unmarried, 7 (10%) indicated that they were divorced or lived apart from their spouse, and 1 person (1%) was widowed. The groups differed only with respect to the number of comorbid diagnoses, which were significantly more frequent in AR (M = 1.89, SD = 0.92) than in WL (M = 1.37, SD = 0.67) [mean difference (MD) = 0.53, 95% CI = 0.1–0.9, p < 0.012]. No significant discrepancies concerning comorbid diagnoses were found between the 2 treatment groups (WE: M = 1.59, SD = 0.82).	**Worry Exposure (WE):** WE treatment also began with psychoeducation. The treatment commenced with self-monitoring of worry. WE began in the 3rd session and continued through the 10th. Concurrently, avoidance and reassurance behaviors were addressed and systematically reduced. The final stage of therapy targeted generalization and relapse prevention. In both treatment conditions, the patients were assigned homework exercises. In WE the homework consisted in practicing WE alone; in AR it focused on learning relaxation skills and then gradually applying them whenever first signs of arousal were noticed. **Wait-list Control (WL):** Randomized in active groups after 15 weeks **Outcomes of Interest:** **S**ymptoms of anxiety and depression, including excessive worrying, negative metacognitive appraisal of worrying and thought suppression. The Hamilton Anxiety Rating Scale and the State-Trait Anxiety Scale were used as primary outcome measures.	**HAMD:** n=27; 13.33±5.31(before); 6.63±5.76 (after); MD= –6.70 (–8.9 to –4.5); p <0.01; **BDI:** n=26 15.22±7.07 (before); 9.38±8.11 (after); MD= –4.48 (–7.3 to –1.6); p <0.01 n=26; 8.43±5.65 (FU 6 mo); n=25; 10.07±6.89 (FU 12 mo) **<u>Worry exposure</u>** **HAMA:** **-** n=29; 21.6±7.23 12.19±7.82; MD= –9.43; CI (–11.9 to –7.0); p=<0.01; **HAMA somatic:** **-** n=29; 8.97±4.72 (before); 5.1 ±4.47 (after); MD= –3.86 (–5.3 to –2.4), p<0.01 **HAMA psychic**: -n= 29; 12.7±3.99 (before); 7.08±3.99 (after); –5.59 (–7.2 to –3.9); p= <0.01 **STAI-T:** -n=26; 51.6±7.93 (before); 45.23±9.55 (after); MD=–6.38 (–9.7 to –3.0), p<0.01 **PSWQ:** n=27; 61.1±.10.40 (before); 54.33±10.13 (after); MD=–6.76 (–9.6 to –3.9) <0.01 -n=23; 50.21±.12.21 (FU 6 mo); -n=26 51.09±.12.62 (FU 12 mo) **MCQ II:** - n=29; 46.4±10.30 (before); 39.05±9.00 (after); MD=–7.38 (–10.1 to –4.6); p<0.01 -n=23; 36.00±.11.36 (FU 6 mo); -n=26; 35.38±.10.38 (FU 12 mo) **WBSI**: - n=27; 55.2±11.00 (before); 46.22±12.20 (after); MD = –8.93 (–12.9 to –4.9); p<0.01 - n=23; 40.91±.14.25 (FU 6 mo); -n=26 41.27±.15.3 (FU 12 mo) **BSI-GSI:**	1. Expert ratings for anxiety symptoms (HAMA) were not conducted at follow-up. Similarly, blinded reviewers did not reassess comorbid diagnoses following treatment 2 The study did not include any psychological placebo condition aside from the WL. 3. Therapists bias **Study ROB**: High due primarily to methodological quality of the study and moderate dropout rate **Author conflict:** Katja Beesdo has received speaking honoraria from Pfizer

Study Details	Study Population	Treatment	Results	Conclusion/Limitations
		Self-report scales of anxiety, worrying and depression including negative metacognition about worrying and thought suppression served as secondary outcome measures	- n=27; 1.00±0.60 (before); -0.66±0.48 (after); -n=23; 0.68±0.68 (FU 6 mo); - n=26; 0.63±0.69 (FU 12 mo) **HAMD;** n=29; 12.4±4.96 (before); 6.07±4.44 (after); MD: –6.28 (–8.0 to –4.6); p <0.01 **BDI**; - n=27; 13.6±7.46 (before); 10.25±7.11; MD= –2.52 (–5.4 to 0.4); p= 0.09 (NS) -n=22; 8.64±7.12 (FU 6 mo); -n=26; 9.42±9.83 (FU 12 mo); **<u>Waiting list control group</u>** **HAMA**: -n=29; 23.33±7.02 (before); 21.15±7.16 (after); **WL:** MD= –2.18; CI (–5.0 to 0.7); p= 0.13; **HAMA somatic:** - n=29; 10.59±4.78(before); 9.02±4.33 (after); MD= –1.56 (–3.2 to 0.0); p= 0.06 (NS) **HAMA psychic:** -n=29; 12.77±3.37 (before); 12.2±3.68 (after); MD: –0.57 (–2.3 to 1.1); p= 0.50 (NS) **STAI-T:** - n=23; 52.91±7.42 (before);52.65±6.88 (after); MD=–0.26 (–2.4 to 1.9); p= 0.80 (NS) **PSWQ:** - n=29; 57.00±7.78 (before); 57.03±9.85 (after); MD=0.27 (–2.3 to 2.9); p=0.83; **MCQII**: - n=29;41.99±8.57(before); 41.68±8.96 (after); MD= –0.30 (–3.2 to 2.6); p=0.83(NS) **WBSI**: - n=29;50.35±9.13(before);48.58±9.04 (after); MD= –1.77 (–4.9 to 1.4); p= 0.26 (NS); **BSI-GSI**: - n=30; 0.68±0.35 (before);0.77±0.37 (after); MD: 0.09 (0.0 to 0.2); p= 0.19 (NS)	

Study Details	Study Population	Treatment	Results	Conclusion/Limitations
			HAMD: -n=29; 14.55±4.82 (before);12.97±4.86 (after); MD= –1.59 (–3.5 to 0.4); p=0.11(NS); **BDI:** -n=28; 13.49±4.65 (before);12.66±5.34 (after); MD= –0.83 (–2.8 to 1.1); p= 0.39 (NS)	
Reference: Conrad et al. 2008 **Purpose:** To show that muscle tension would be elevated initially in GAD and that progress in treatment would go hand in hand with a reduction in muscle tension **Setting:** Stanford University and VA Palo Alto Health Care System. Patients were recruited in Peninsula and South Bay region of the San Francisco Bay Area. **F/u:** 6 weeks **Funding source:** This research was supported by grants from the National Institutes of Health (MH066953-01) and the Department of Veterans Affairs (ROT0042825)	**Number of patients:** AR or WLC (n=49); NAC (n=21). **Inclusion criteria:** The patient should meet DSM-IV criteria for GAD as primary diagnosis, and the diagnosis had to be identified as the most important source of current distress. If on benzodiazepines, participants were included only if the dose was stable and less than 1.5 mg/day in the month preceding the assessment **Exclusion criteria:** Patients with a history of bipolar disorder, psychosis, or other delusional disorders, substance or alcohol abuse or dependence within the last year, a serious medical illness within three months, and heart disease, diabetes, significant asthma, emphysema, or any other diseases that might affect the physiological systems	**Intervention**: Number of sessions (12); time (60 min); duration (12 weeks) Applied Relaxation (AR) and Wait-list control (WLC); The WLC group began treatment immediately after the fifth Relaxation Test and were treated into AR group. GAD patients were randomized to weekly relaxation therapy sessions for 12 weeks (AR) or to the waiting list control condition (WLC). The AR group completed the Relaxation Test and questionnaires before Session 2, Session 5, Session 10, 1 week after Session 12, and 7 weeks after Session 12 (6-week follow-up). The WLC group completed the first five Relaxation Tests and questionnaires at corresponding times, and then began AR. **Outcomes of Interest:** anxiety, worry, stress, relaxation, cognitive and	**Pretreatment Analyses** At pretreatment, there *were no notable differences between the AR and WLC groups* on any of the questionnaires or the psychological and physiological measures of the Relaxation Test. **Posttreatment Improvement** For the primary outcome measures, there were significant self-ratings of anxiety, F (4,139.56) =2.99, P=.02, worry, F (4,137.03) =2.58, p=.04, and perceived stress, F (4,137.87) =4.59, p=.002, with the *AR group improving more than the WLC group.* **-ESs for the primary outcome measures ranged from 0.25 to 1.13.** There was more improvement in the AR than in the WLC group in all secondary outcome measures except for the BDI. There were adverse reactions to relaxation, F (1,31.73) =7.67, p=.009, in that these reactions decreased more with treatment in AR than in WLC. **-ESs for the secondary outcome measures ranged from 0.03 to 0.95**. Participants in the WLC group were sleepier than their AR counterparts, F (1,88.20) =17.26, po.001, and sleepiness in the WLC group increased faster than in the AR participants, F (2,998.25) =5.95, =.003. **Posttreatment and follow-up** showed a significant effect of progress only for the self-	**Conclusion:** There was significantly more improvement in AR than in WLC in 50% of the primary outcome measures in the completer analysis at posttreatment, 53% of AR participants were considered clinically significantly improved. The clinical effects of AR in improving GAD symptoms are moderate at most and cannot be attributed to reducing muscle tension or autonomic activation. Muscle relaxation therapies (MRT) training may work more on a cognitive–psychological than on a physiological level like other relaxation therapies such as yoga and mindfulness-meditation. The study concluded that muscle tension is not elevated initially in GAD patients, and that the treatment does not result in a reduction in muscle tension (failed hypothesis). There is scant evidence that

Study Details	Study Population	Treatment	Results	Conclusion/Limitations
awarded to Dr. Roth.	under scrutiny. NACs were to be psychiatrically and physically healthy and to match the patient group in gender and age. Participants were not to have had a history of relaxation or meditation practice. **Pt. baseline characteristics:** Women: 57% in GAD and 62% in NAC group. Age range from 43-46 years, and 84% Caucasian in GAD and 57% in NAC group. Fifty-nine percent of GAD patients and 38% of non-anxious controls were taking medications, often more than one. Twenty percent of GAD patients were taking anxiolytics and 20% antidepressants. Ten percent of GAD patients and 10% of non-anxious controls were taking thyroid medications. Ten percent of GAD patients and 14% of non-anxious controls were taking lipid-lowering agents. Twenty percent of GAD patients and 19% of non-anxious controls were taking antihypertensives.	somatic anxiety symptoms, depressive symptoms	rating for anxiety F (1,16.89) =4.87, p=.04, which was rated worse at follow-up than posttreatment. There was a trend toward ratings of worse worry during follow-up than posttreatment; p=.06. - **At posttreatment.53% of AR patients compared to 7% of WLC participants met criteria for clinically significant improvement** **-At follow-up, 29% of AR and 0% of WLC participants met criteria for clinically significant improvement in the completer analysis.**	GAD patients learn to relax muscles over the course of therapy by acquiring a skill that they could apply when muscle tension rose in daily life to higher levels. **Limitations: 1.** Neglect to include an instructed worry period in the laboratory assessment. 2. Laboratory measurements of muscle tension may not adequately represent tension outside the laboratory. 3. The psychophysiological data may also have been affected to some extent by medication use. 4. Diagnostic reliability issues, 5. Comparator is not a control group, 6. The ADIS interview was not conducted after completion of treatment 7. The WLC group wait did not complete a follow-up assessment when the AR did, but began treatment immediately after the fifth Relaxation Test; 8. Confounding of the diagnosis with treatment data **Study ROB**: High **Author conflict:** No

Study Details	Study Population	Treatment	Results	Conclusion/Limitations
	Sixty-five percent of GAD patients had additional DSM-IV diagnoses			

Table 4. Cochrane Risk of Bias 2.0 Tool for RCTs on Relaxation Therapy to Treat GAD

Reference	Dugas et al., (2010)	Hayes-Skelton et al., (2013)	Janbozorgi et al., (2009)	Hoyer et al., (2009)	Conrad et al., (2008)
• Was the allocation sequence generated adequately (e.g., random number table, computer-generated randomization)?	Yes	Yes	Yes	Yes	Yes
• Was the allocation of treatment adequately concealed (e.g., pharmacy-controlled randomization, concealed envelopes)?	Yes	Yes	NI	Yes	Yes
• Did baseline difference between study groups suggest a problem with randomization?	No	No	No	PY	No
Overall RoB for Randomization Process	**Low**	**Low**	**Some concerns**	**Some concerns**	**Low**
Deviation from Intended Intervention (Effect of Assignment)					
• Were participants aware of their assigned intervention during the trial?	Yes	NI	Yes	NI	PY
• Were providers and people delivering treatment aware of assigned intervention during trial?	No	No	Yes	No	No
• Were there deviations from the intended intervention that arose because of the experimental context?	No	No	NI	No	NI
• Were these deviations from intended intervention balanced between groups?	NA	NA	NA	No	No
• Were these deviations likely to have affected the outcome?	NA	NA	NA	PN	No
• Was an appropriate analysis used to estimate the effect of assignment to intervention?	Yes	Yes	Yes	Yes	Yes
Overall RoB of Effect of Assignment	**Low**	**Low**	**Some concerns**	**Some concerns**	**Some concerns**
Missing Outcome Data					
• Were data for this outcome available for all, or nearly all, participants randomized?	Yes	Yes	Yes	Yes	Yes
• Is there evidence that result was not biased by missing outcome data?	NA	Yes	NI	Yes	PY

Reference	Dugas et al., (2010)	Hayes-Skelton et al., (2013)	Janbozorgi et al., (2009)	Hoyer et al., (2009)	Conrad et al., (2008)
• Could missingness in the outcome depend on its true value?	NA	NA	NI	NA	NA
• Do the proportions of missing outcome data differ between intervention groups?	NA	NA	Yes	PY	Yes
• Is it likely that missingness in the outcome depended on its true value?	NA	NA	NI	NA	NA
Overall RoB of Missing Data	**Low**	**Low**	**Some concerns**	**Some concerns**	**Some concerns**
Measurement of the Outcome					
• Was the method of measuring the outcome inappropriate?	No	No	No	No	No
• Could measurement or ascertainment of the outcome have differed between intervention groups?	No	No	No	No	No
• Were outcome assessors aware of the intervention received by study participants?	No	No	NI	No	No
• Could assessment of the outcome have been influenced by knowledge of intervention received?	No	Yes	NI	No	No
• Is it likely that assessment of the outcome was influenced by knowledge of intervention received?	No	No	NI	No	No
Overall RoB of Measurement of Outcome	**Low**	**Some concerns**	**Some concerns**	**Low**	**Low**
Selection of Reported Results					
• Was the trial analyzed in accordance with a pre-specified plan that was finalized before unblinded outcome data were available for analysis?	NI	PY	NI	PY	Yes
Overall RoB of Reported Results	**Some Concerns**	**Some Concerns**	**Some concerns**	**Low**	**Low**
Overall Study RoB	**Some concerns**	**Some concerns**	**High**	**High**	**High**

*Responses: Y=Yes; PY=Probably Yes; N=No; PN=Probably No; NA=Not Applicable; NI=No Information; RoB: risk of bias

Table 5. Cochrane Risk of Bias 2.0 Overall Risk of Bias Judgement

Category	Definition
Low risk of bias	The study is judged to be at **low risk of bias for all domains** for this result.
Some concerns	The study is judged to be at **some concerns** in at least one domain for this result.
High risk of bias	The study is judged to be at **high risk of bias** in at least one domain for this result. OR The study is judged to have **some concerns** for **multiple domains** in a way that substantially lowers confidence in the result.

References

Conrad, A., Isaac, L., & Roth, W. T. (2008). The psychophysiology of generalized anxiety disorder: 2. effects of applied relaxation. *Psychophysiology*, *45*(3), 377–388. https://doi.org/10.1111/j.1469-8986.2007.00644.x

Dugas, M. J., Brillon, P., Savard, P., Turcotte, J., Gaudet, A., Ladouceur, R., … Gervais, N. J. (2010). A randomized clinical trial of cognitive-behavioral therapy and applied relaxation for adults with generalized anxiety disorder. *Behavior Therapy*, *41*(1), 46–58. https://doi.org/10.1016/j.beth.2008.12.004

Hayes-Skelton, S. A., Roemer, L., & Orsillo, S. M. (2013). A randomized clinical trial comparing an acceptance-based behavior therapy to applied relaxation for generalized anxiety disorder. *Journal of Consulting and Clinical Psychology*, *81*(5), 761–773. https://doi.org/10.1037/a0032871

Hoyer, J., Beesdo, K., Gloster, A. T., Runge, J., Höfler, M., & Becker, E. S. (2009). Worry exposure versus applied relaxation in the treatment of generalized anxiety disorder. *Psychotherapy and Psychosomatics*, *78*(2), 106–115. https://doi.org/10.1159/000201936

Janbozorgi, M., Zahirodin, A., Norri, N., Ghafarsamar, R., & Shams, J. (2009). Providing emotional stability through relaxation training. *Eastern Mediterranean Health Journal*, *15*(3), 629–638.

Appendix A

Inclusion Criteria:

- **Publications type:** Systematic reviews (SRs) and randomized controlled clinical trials (RCTs) published in English language in peer reviewed journals.
- **Search date:** 01/01/2008 to present
- **Population:** Adults 18 years or older meeting diagnostic criteria for GAD
- **Intervention (s):**
    - Complementary and integrative health (CIH) and other non-pharmacologic treatments: music therapy; equine therapy; training and caring for service dogs; yoga therapy; tai chi; acupuncture therapy; meditation therapy; outdoor sports therapy; hyperbaric oxygen therapy; accelerated resolution therapy; art therapy; magnetic stimulation therapy; massage; healing touch; therapeutic touch; cannabinoids; chiropractic care
    - Pharmacological treatments: SSRIs (fluoxetine, paroxetine, escitalopram, and sertraline); SNRIs (duloxetine, venlafaxine); buspirone, hydroxyzine, benzodiazepines (diazepam, lorazepam, alprazolam, clonazepam, quetiapine); tricyclic antidepressants (imipramine); atypical antidepressants (trazodone); tetracyclic antidepressants (mirtazapine); NDRI (bupropion); anticonvulsant (pregabalin); serotonin modulator (vortioxetine)
    - Psychological treatments: CBT; Cognitive Therapy; Applied Relaxation
- **Outcomes:** quality of life; functional status; patient satisfaction; anxiety; insomnia; pain; anxiety
- **Timing:** no minimum follow-up
- **Setting(s):** primary care; specialty care; general mental health care

Exclusion Criteria:

- **Wrong publication type**: narrative review article, case reports editorial, commentary, protocol of randomized trial without results, any article without original data, abstract alone.
- **Wrong study design:** Observational study (for example, cohort study, case control study, cross-sectional study); treatment study without randomization, randomized study with less than 20 patients (10 per study group).
- **Wrong population**: animal studies, children or adolescents less than 18 years of age (studies must have enrolled a patient population in which at least 80% of patients were diagnosed with GAD.
- **Wrong language:** Study in language other than English.
- **Wrong or no intervention:** CIH treatments other than those listed in inclusion criteria; medications other than those listed in inclusion criteria; psychological treatments other than those listed in inclusion criteria
- **Wrong comparator:** CIH treatments other than those listed in inclusion criteria; medications other than those listed in inclusion criteria; psychological treatments other than those listed in inclusion criteria
- **Wrong outcome(s):** Any study that does not have at least one of the included outcomes of interest. Any subjective outcome (e.g. symptoms; quality of life) not measured using a validated instrument.

Appendix B

Table 1. Studies Excluded at Data Abstraction Level

Authors	Reason for Exclusion
Exercise	
Herring, Jacob, Suveg & O'Connor, 2011	Duplicate
Massage	
Sherman et al. 2010	Wrong comparator
Relaxation Therapy	
Donegan & Dugas, 2012	Wrong study design
Transcranial Magnetic Stimulation (TMS)	
Difenbach, Assaf, Gothe, Gueroguieva & Tolin, 2016	Wrong outcome(s)

References

Diefenbach, G. J., Assaf, M., Goethe, J. W., Gueorguieva, R., & Tolin, D. F. (2016). Improvements in emotion regulation following repetitive transcranial magnetic stimulation for generalized anxiety disorder. *Journal of Anxiety Disorders*, *43*, 1–7. https://doi.org/10.1016/j.janxdis.2016.07.002

Donegan, E., & Dugas, M. J. (2012). Generalized anxiety disorder: a comparison of symptom change in adults receiving cognitive-behavioral therapy or applied relaxation. *Journal of Consulting and Clinical Psychology*, *80*(3), 490–496. https://doi.org/10.1037/a0028132

Herring, M. P., Jacob, M. L., Suveg, C., & O'Connor, P. J. (2011). Effects of short-term exercise training on signs and symptoms of generalized anxiety disorder. *Mental Health and Physical Activity*, *4*(2), 71–77. https://doi.org/10.1016/j.mhpa.2011.07.002

Sherman, K. J., Ludman, E. J., Cook, A. J., Hawkes, R. J., Roy-Byrne, P. P., Bentley, S., … Cherkin, D. C. (2010). Effectiveness of therapeutic massage for generalized anxiety disorder: a randomized controlled trial. *Depression and Anxiety*, *27*(5), 441–450. https://doi.org/10.1002/da.20671

Appendix C

See **Figures 4, 5 and 6** below for bubble maps. Bubble maps provide a visual overview of the distribution of evidence for the complementary and integrative health and other interventions included in these systematic reviews. The bubble maps display information about the research meeting the inclusion and exclusion criteria (see Appendix A) for these reviews and include the following:

- **The strength of evidence** (y-axis)
  - The y-axis provides an overview of the quantity of research for an intervention. For this estimate, we used the number of individual RCTs and/or the number of RCTs included in previously published systematic reviews. The color of the bubbles indicates the strength of evidence (SOE). The lighter the color of a bubble, the higher the SOE and vice versa.
- **The direction of findings** (x-axis)
  - The x-axis provides an estimate of the clinical effectiveness of an intervention with the bubble maps differentiating the findings with three different categories, which are, "favors control"; "no difference"; and "favors intervention". Control groups are important to consider and have been noted in the maps as well, given that some studies have an active control and others do not.
- **The confidence in the reported effect** (bubble size)
  - The size of a bubble indicates the level of confidence in the reported effect. Next to each bubble we abbreviate the intervention, the control group, and note the number of studies conducted.

It is important to note that, due to the number of studies included and the scope of these systematic reviews, the bubble maps may only represent limited information.

Figure 4. Bubble Plot of Findings for Anxiety Symptoms

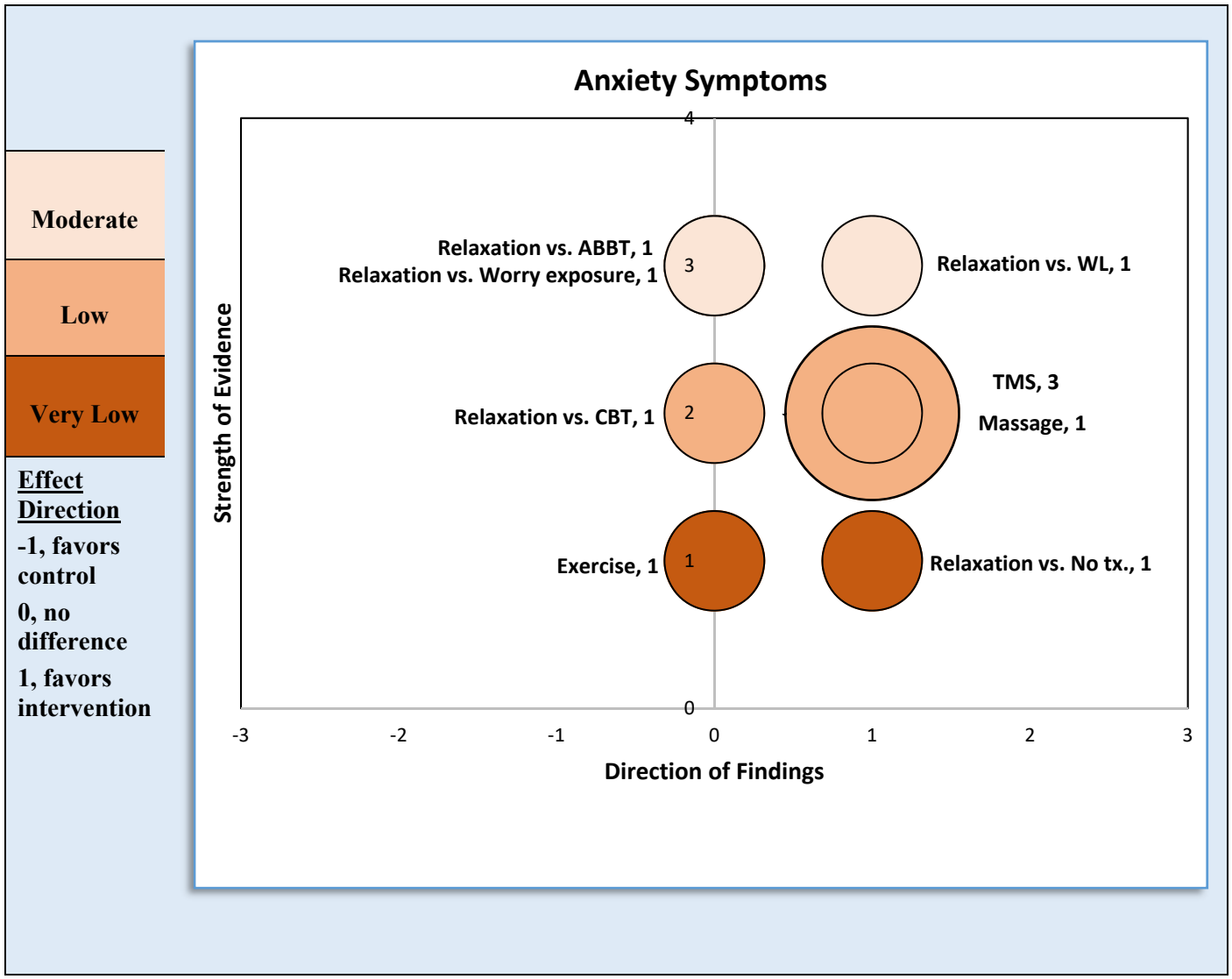

Figure 5. Bubble Plot of Findings for Depression Symptoms

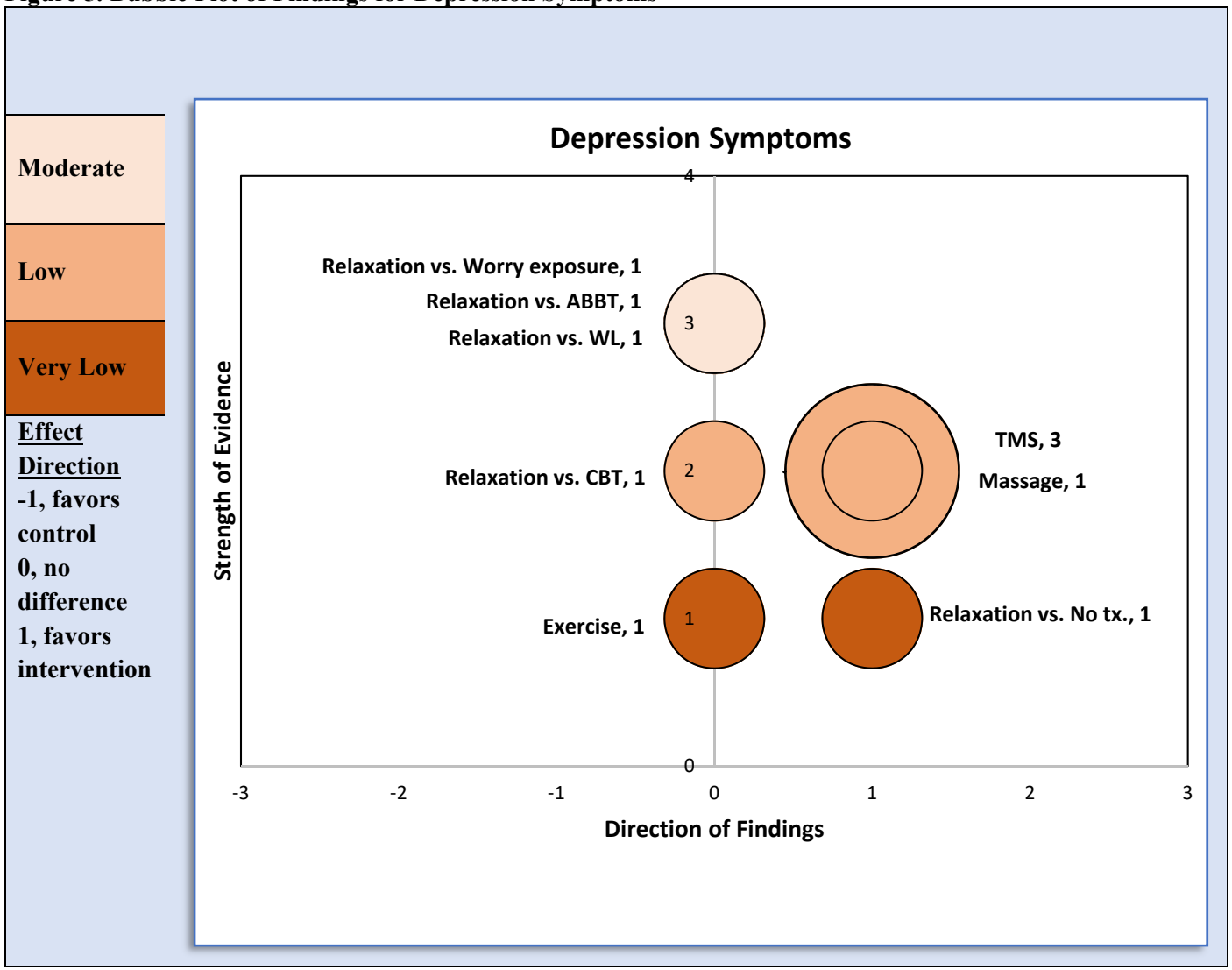

Figure 6. Bubble Plot of Findings for Worry Symptoms