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Biofeedback for treatment of irritable bowel syndrome (Review)

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[Intervention Review]

Biofeedback for treatment of irritable bowel syndrome

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ABSTRACT

Background

Irritable bowel syndrome (IBS) is a prevalent condition that currently lacks highly effective therapies for its management. Biofeedback has been proposed as a therapy that may help individuals learn to exert conscious control over sympatho-vagal balance as an indirect method of symptom management.

Objectives

Our primary objective was to assess the efficacy and safety of biofeedback-based interventions for IBS in adults and children.

Search methods

We searched the Cochrane Inflammatory Bowel Disease (IBD) Group Specialized Trials Register, Cochrane Central Register of Controlled Trials (CENTRAL), MEDLINE, EMBASE, the Cumulative Index to Nursing and Allied Health Literature (CINAHL), and the Allied and Complementary Medicine Database (AMED) from inception to 24 July 2019. We also searched reference lists from published trials, trial registries, device manufacturers, conference proceedings, theses, and dissertations.

Selection criteria

We judged randomized controlled trials to be eligible for inclusion if they met the Association for Applied Psychophysiology and Biofeedback definition of biofeedback, and if they compared a biofeedback intervention to an active, sham, or no-treatment control for the management of IBS.

Data collection and analysis

Two authors independently screened trials for inclusion, extracted data, and assessed risk of bias. Primary outcomes were IBS global or clinical improvement scores and overall quality of life measures. Secondary outcome measures were adverse events, assessments of stool frequency and consistency, changes in abdominal pain, depression, and anxiety. For dichotomous outcomes, we calculated the risk ratio (RR) and 95% confidence interval (CI). For continuous outcomes, we calculated the mean difference (MD) and 95% CI. We used GRADE criteria to assess the overall certainty of the evidence.

Main results

We identified eight randomized trials with a total of 300 adult participants for our analysis. We did not identify any trials in children. Four trials assessed thermal biofeedback. One trial assessed rectosigmoidal biofeedback. Two trials assessed heart rate variability biofeedback. Two trials assessed electrocutaneous biofeedback. Comparators were: no treatment (symptom monitoring group; three studies), attention control (pseudomeditation; two studies), relaxation control (one study), counseling (two studies), hypnotherapy (one study), standard therapy (one study), and sham biofeedback (one study). We judged all trials to have a high or unclear risk of bias.

Global/Clinical improvement

The clinical benefit of biofeedback plus standard therapy compared to standard therapy alone was uncertain (RR 4.20, 95% CI 1.40 to 12.58; 1 study, 20 participants; very low-certainty evidence). The same study also compared biofeedback plus standard therapy to sham biofeedback plus standard therapy. The clinical benefit in the biofeedback group was uncertain (RR 2.33, 95% CI 1.13 to 4.80; 1 study, 20 participants; very low-certainty evidence).

The clinical benefit of heart rate biofeedback compared to hypnotherapy was uncertain when measured with the IBS severity scoring system (IBS-SSS) (MD -58.80, 95% CI -109.11 to -8.49; 1 study, 61 participants; low-certainty evidence). Compared to counseling, the effect of heart rate biofeedback was unclear when measured with a composite symptom reduction score (MD 7.03, 95% CI -51.07 to 65.13; 1 study, 29 participants; low-certainty evidence) and when evaluated for clinical response (50% improvement) (RR 1.09, 95% CI 0.48 to 2.45; 1 study, 29 participants; low-certainty evidence).

The clinical benefit of thermal biofeedback used in a multi-component psychological intervention (MCPI) compared to no treatment was uncertain when measured with a composite clinical symptom reduction score (MD 30.34, 95% CI 8.47 to 52.21; 3 studies, 101 participants; very low-certainty evidence), and when evaluated as clinical response (50% improvement) (RR 2.12, 95% CI 1.24 to 3.62; 3 studies, 101 participants; very low-certainty evidence). Compared to attention control, the effects of thermal biofeedback within an MCPI were unclear when measured with a composite clinical symptom reduction score (MD 4.02, 95% CI -21.41 to 29.45; 2 studies, 80 participants; very low-certainty evidence) and when evaluated as clinical response (50% improvement) (RR 1.10, 95% CI 0.72 to 1.69, 2 studies, 80 participants; very low-certainty evidence).

Quality of life

A single trial used overall quality of life as an outcome measure, and reported that both the biofeedback and cognitive therapy groups improved after treatment. The trial did not note any between-group differences, and did not report any outcome data.

Adverse events

Only one of the eight trials explicitly reported adverse events. This study reported no adverse events in either the biofeedback or cognitive therapy groups (RD 0.00, 95% CI -0.12 to 0.12; 29 participants; low-certainty evidence).

Authors' conclusions

There is currently not enough evidence to assess whether biofeedback interventions are effective for controlling symptoms of IBS. Given the positive results reported in small trials to date, biofeedback deserves further study in people with IBS. Future research should include active control groups that use high provider-participant interaction, in an attempt to balance non-specific effects of interventions between groups, and report both commonly used outcome measures (e.g. IBS-SSS) and historical outcome measures (e.g. the composite primary symptom reduction (CPSR) score) to allow for meta-analysis with previous studies. Future studies should be explicit in their reporting of adverse events.

PLAIN LANGUAGE SUMMARY

Biofeedback for the treatment of irritable bowel syndrome

Review Question

We reviewed the evidence for the effect of biofeedback therapy on the management of irritable bowel syndrome (IBS).

Background

IBS is a common disorder that includes both abdominal pain and changes in stool frequency or consistency. Biofeedback is a therapy in which participants use technology to track a process that is not normally under conscious control (e.g. heart rate, tension of the anal sphincter) in order to see how relaxed states of mind affect these measures. Researchers have proposed that achieving more relaxed states through the tool of biofeedback may help to improve the symptoms of IBS.

Study Characteristics

We searched for studies that compared biofeedback to either no treatment, sham treatment, or to other active treatments for IBS. We reviewed eight trials that included 300 total participants and assessed the effect of biofeedback on IBS. Each of these studies only included adults, and was carried out in an outpatient setting. The studies ranged from eight weeks to six months in length. The types of biofeedback devices varied, and included heart rate variability, measures of skin temperature or electrical resistance, and the tension of the muscles of the anus.

Study Funding Sources

None of the included trials disclosed funding sources.

Key Results

Our primary clinical outcomes were global clinical improvement and quality of life.

Regarding overall improvement, three trials compared biofeedback to no treatment and found that biofeedback as part of a relaxation training program led to better symptom control than no treatment (very low-certainty evidence). Two of these trials also compared biofeedback to an attention control and found minimal symptom improvement, but the effects of chance could not be ruled out because the evidence was of very low-certainty. One trial found a greater symptom benefit with heart rate biofeedback compared to hypnotherapy (low-certainty evidence). Of two trials comparing biofeedback to counseling, any apparent effect was minimal and the effect of chance could not be ruled out (very low-certainty evidence). When rectosigmoidal biofeedback was compared to relaxation control, the effect favored the relaxation control. The addition of biofeedback to standard medical therapy was superior to medical therapy alone and to medical therapy plus sham biofeedback (low-certainty evidence for both findings).

Quality of Life

A single trial looked specifically at overall quality of life. Quality of life improved both for those in the biofeedback group and those in the cognitive therapy group, but there was no overall difference between groups.

Adverse Events

Only one trial explicitly reported on adverse events. It reported no adverse events in either the biofeedback group or the cognitive therapy group.

Certainty of the Evidence

We used the GRADE criteria to assess the certainty of the evidence for each of these findings. These ranged from low to very low.

The evidence is current up to July 2019.

Authors' Conclusions

We conclude that the existing data on biofeedback for IBS are limited and leave us uncertain about its value in IBS symptom management. The studies currently available all have design limitations that make the results difficult to apply to clinical settings. We do, however, recommend further study in this area, as biofeedback could represent a unique approach for a difficult to manage condition.

SUMMARY OF FINDINGS

Summary of findings for the main comparison. Biofeedback plus standard therapy compared to standard therapy for irritable bowel syndrome

Biofeedback plus standard therapy compared to standard therapy for irritable bowel syndrome

Patient or population: people with irritable bowel syndrome
Setting: outpatient setting
Intervention: biofeedback plus standard therapy
Comparison: standard therapy

Outcomes	Anticipated absolute effects* (95% CI)		Relative effect (95% CI)	№ of participants (studies)	Certainty of the evidence (GRADE)	Comments
	Risk with standard therapy	Risk with biofeedback plus standard therapy				
Clinical response (adequate improvement or remission) follow-up: 6 months	Study population 200 per 1,000	 840 per 1,000 (280 to 1,000)	RR 4.20 (1.40 to 12.58)	20 (1 RCT)	⊕⊖⊖⊖ VERY LOW [a b]	
Quality of life (QoL)	No formal quality of life scales were used in the included trial.		-	-	-	
Adverse events (AE)	Adverse events were not reported in this study.		-	-	-	
Serious adverse events (SAE)	Serious adverse events were not reported in this study.		-	-	-	
Abdominal pain (Pain) assessed with: diaries Scale from: 0 to 4 Lower score = better	Biofeedback plus standard therapy: mean pain scores reduced from 2.2 to 0.0 after 1 month and 0.6 after 6 months. Standard therapy: mean pain scores reduced from 2.2 to 0.6 after 1 month and 1.2 after 6 months.		-	20 (1 RCT)	⊕⊖⊖⊖ VERY LOW [a c d]	No SD or P values were provided

*__The risk in the intervention group__ (and its 95% confidence interval) is based on the assumed risk in the comparison group and the __relative effect__ of the intervention (and its 95% CI).

CI: Confidence interval; **RR:** Risk ratio; **RCT:** randomized controlled trial; **SD** = standard deviation

GRADE Working Group grades of evidence
High certainty: We are very confident that the true effect lies close to that of the estimate of the effect
Moderate certainty: We are moderately confident in the effect estimate: The true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different
Low certainty: Our confidence in the effect estimate is limited: The true effect may be substantially different from the estimate of the effect

Very low certainty: We have very little confidence in the effect estimate: The true effect is likely to be substantially different from the estimate of effect

[a]Downgraded one level for study limitations: lack of blinding and inadequately described protocols lead us to consider this a high risk of bias study.
[b] Downgraded two levels for imprecision: a single small study with a confidence interval that includes both a small and very large effect of intervention.
[c] Downgraded one level for imprecision: CI not estimable.
[d] Downgraded an additional level for study limitations: measures of variation and statistical significance were not reported.

Summary of findings 2. Biofeedback plus standard therapy compared to sham biofeedback plus standard therapy for irritable bowel syndrome

Biofeedback plus standard therapy compared to sham biofeedback plus standard therapy for irritable bowel syndrome

Patient or population: people with irritable bowel syndrome
Setting: outpatient setting
Intervention: biofeedback plus standard therapy
Comparison: sham biofeedback plus standard therapy

Outcomes	Anticipated absolute effects* (95% CI)		Relative effect (95% CI)	№ of participants (studies)	Certainty of the evidence (GRADE)	Comments
	Risk with sham biofeedback plus standard therapy	Risk with biofeedback plus standard therapy				
Clinical response (adequate improvement or remission) follow-up: 6 months	Study population 400 per 1,000	 932 per 1,000 (452 to 1,000)	RR 2.33 (1.13 to 4.80)	20 (1 RCT)	⊕⊖⊖⊖ VERY LOW [a b]	
Quality of life (QoL)	No formal quality of life scales were used in the included trial.		-	-	-	
Adverse events (AE)	Adverse events were not reported in this study.		-	-	-	
Serious adverse events (SAE)	Serious adverse events were not reported in this study.		-	-	-	
Abdominal pain (Pain) Scale from: 0 to 4 Lower score = better	Biofeedback plus standard therapy: mean pain scores reduced from 2.2 to 0.0 after one month and 0.6 after six months. Sham biofeedback plus standard therapy: mean pain scores reduced from 2.1 to 0.6 after one month and 1.0 after six months.		-	20 (1 RCT)	⊕⊖⊖⊖ VERY LOW [a c d]	No SD or P values were provided

*__The risk in the intervention group__ (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).

CI: Confidence interval; **RR:** Risk ratio; **RCT:** randomized controlled trial; **SD** = standard deviation

GRADE Working Group grades of evidence
High certainty: We are very confident that the true effect lies close to that of the estimate of the effect
Moderate certainty: We are moderately confident in the effect estimate: The true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different
Low certainty: Our confidence in the effect estimate is limited: The true effect may be substantially different from the estimate of the effect
Very low certainty: We have very little confidence in the effect estimate: The true effect is likely to be substantially different from the estimate of effect

[a] Downgraded one level for study limitations: inadequately reported methods lead us to consider this a high risk of bias study.
[b] Downgraded two levels for imprecision: a single small study with a confidence interval that includes both a small and very large effect of intervention.
[c] Downgraded one level for imprecision: CI not estimable.
[d] Downgrading an additional level for study limitations: measures of variation and statistical significance were not reported.

Summary of findings 3. Biofeedback compared to hypnotherapy for irritable bowel syndrome

Biofeedback compared to hypnotherapy for irritable bowel syndrome

Patient or population: people with irritable bowel syndrome
Setting: outpatient setting
Intervention: biofeedback
Comparison: hypnotherapy

Outcomes	Anticipated absolute effects* (95% CI)		Relative effect (95% CI)	№ of participants (studies)	Certainty of the evidence (GRADE)	Comments
	Risk with hypnotherapy	Risk with biofeedback				
Clinical symptoms (Improvement) assessed with: IBS-SSS Lower score = better follow-up: 12 weeks	The mean score with hypnotherapy control was 58.0 lower	MD 58.8 lower (109.11 lower to 8.49 lower)	-	61 (1 RCT)	⊕⊕⊖⊖ LOW [a b]	
Quality of life (QoL)	Quality of life is included in the IBS-SSS outcome but is not reported separately in this study.		-	-	-	
Adverse events (AE)	Adverse events were not reported in this study.		-	-	-	
Serious adverse events (SAE)	Serious adverse events were not reported in this study.		-	-	-	

Abdominal pain (Pain)	Abdominal pain is included in the IBS-SSS outcome but is not reported separately in this study.		-	-	-
Depression assessed with: depression sub-score of the HADS Lower score = better	The mean score with hypnotherapy control was 5.9	MD 1.0 lower (3.18 lower to 1.18 higher)	-	61 (1 RCT)	⊕⊕⊖⊖ LOW [a c]
Anxiety assessed with: anxiety sub-score of the HADS Lower score = better	The mean score with hypnotherapy control was 9.1	MD 0.7 higher (1.68 lower to 3.08 higher)	-	61 (1 RCT)	⊕⊕⊖⊖ LOW [a c]

*__The risk in the intervention group__ (and its 95% confidence interval) is based on the assumed risk in the comparison group and the __relative effect__ of the intervention (and its 95% CI).

CI: Confidence interval; **MD:** mean difference; **RCT:** randomized controlled trial; **IBS-SSS:** IBS severity scoring system; **HADS:** hospital anxiety and depression scale

GRADE Working Group grades of evidence
High certainty: We are very confident that the true effect lies close to that of the estimate of the effect
Moderate certainty: We are moderately confident in the effect estimate: The true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different
Low certainty: Our confidence in the effect estimate is limited: The true effect may be substantially different from the estimate of the effect
Very low certainty: We have very little confidence in the effect estimate: The true effect is likely to be substantially different from the estimate of effect

[a] Downgraded one level for study limitations: overall high risk of bias.
[b] Downgraded one level for imprecision: a single small study with a confidence interval that includes both a very large and very small effect.
[c] Downgraded one level for imprecision: a single small study with a confidence interval that spans no effect.

Summary of findings 4. Biofeedback compared to counseling for irritable bowel syndrome

Biofeedback compared to counseling for irritable bowel syndrome

Patient or population: people with irritable bowel syndrome
Setting: outpatient setting
Intervention: biofeedback
Comparison: counseling

Outcomes	Anticipated absolute effects* (95% CI)		Relative effect	№ of participants (studies)	Certainty of the evidence	Comments
	Risk with counseling	Risk with biofeedback				

			(95% CI)		(GRADE)	
Composite Primary Symptom Reduction Score (CPSR) Scale from: -100 to 100 Higher score = better	The mean score with counseling control was 31.46	MD 7.03 higher (51.07 lower to 65.13 higher)	-	29 (1 RCT)	⊕⊕⊖⊖ LOW [a b]	
Clinical response assessed with: 50% improvement in composite symptom score	Study population		RR 1.09 (0.48 to 2.45)	29 (1 RCT)	⊕⊕⊖⊖ LOW [a b]	
	429 per 1,000	467 per 1,000 (206 to 1,000)				
Quality of life (QoL) assessed with: IBSIS	Both the biofeedback and cognitive therapy groups improved after treatment but there were no between group differences noted. No outcomes data reported.		-	29 (1 RCT)	⊕⊖⊖⊖ VERY LOW [f]	
Adverse events (AE) assessed with: self report		RD 0 (0.12 fewer to 0.12 more)	-	29 (1 RCT)	⊕⊕⊖⊖ LOW [c d]	No events occurred in either group
Serious adverse events (SAE)		RD 0 (0.12 fewer to 0.12 more)	-	29 (1 RCT)	⊕⊕⊖⊖ LOW [c d]	No events occurred in either group
Abdominal pain (Pain) Scale from: 0 to 4 Lower score = better	The mean score with counseling control was 0.65	MD 0.04 higher (0.43 lower to 0.52 higher)	-	29 (1 RCT)	⊕⊕⊖⊖ LOW [a e]	

*__The risk in the intervention group__ (and its 95% confidence interval) is based on the assumed risk in the comparison group and the __relative effect__ of the intervention (and its 95% CI).

CI: Confidence interval; **RR:** Risk ratio; **MD**: mean difference; **RCT:** randomized controlled trial

GRADE Working Group grades of evidence
High certainty: We are very confident that the true effect lies close to that of the estimate of the effect
Moderate certainty: We are moderately confident in the effect estimate: The true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different
Low certainty: Our confidence in the effect estimate is limited: The true effect may be substantially different from the estimate of the effect

Very low certainty: We have very little confidence in the effect estimate: The true effect is likely to be substantially different from the estimate of effect

[a] Downgraded one level for study limitations: unclear reporting and high dropout rates led us to consider this a high risk of bias study.
[b] Downgraded one level for imprecision: the confidence interval is wide and includes no effect.
[c] Downgraded one level for possible publication bias: presumably AE would be measured in all trials, yet only one reported explicitly on them.
[d] Downgraded one level for imprecision: while the CI is narrow, the total number of participants is low (n = 29) and the CI includes no effect.
[e] Downgraded one level for imprecision: while the CI is narrow, the total number of participants is low (n = 29).
[f] Downgraded two levels for study limitations (the study is at high risk of bias and the outcome is incompletely reported) and one level for serious imprecision (small sample size).

Summary of findings 5. Multi-component psychological intervention (with biofeedback) compared to no-treatment control for irritable bowel syndrome

Multi-component psychological intervention (with biofeedback) compared to no-treatment control for irritable bowel syndrome

Patient or population: people with irritable bowel syndrome
Setting: outpatient setting
Intervention: multi-component psychological intervention (with biofeedback)
Comparison: no-treatment control

Outcomes	Anticipated absolute effects* (95% CI)		Relative effect (95% CI)	№ of participants (studies)	Certainty of the evidence (GRADE)	Comments
	Risk with no-treatment control	Risk with multi-component psychological intervention (with biofeedback)				
Composite Primary Symptom Reduction Score (CPSR) Scale from: -100 to 100 higher score = better follow-up: 8 weeks	The mean score with no treatment ranged from 6.4 to 15.4	MD 30.34 higher (8.47 higher to 52.21 higher)	-	101 (3 RCTs)	⊕⊖⊖⊖ VERY LOW a b c	
Clinical Response assessed with: 50% improvement in composite symptom score follow-up: 8 weeks	Study population		RR 2.12 (1.24 to 3.62)	101 (3 RCTs)	⊕⊖⊖⊖ VERY LOW a b c	
	260 per 1,000	551 per 1,000 (322 to 941)				
Quality of life (QoL)	No formal quality of life scales were used in the included trials.		-	-	-	
Adverse events (AE)	Adverse events were not reported in these studies.		-	-	-	
Serious adverse events (SAE)	Serious adverse events were not reported in these studies.		-	-	-	

Abdominal pain (Pain) assessed with: symptom diaries Lower score = better follow-up: 8 weeks	The mean score with no treatment ranged from 9.1 to 22.0	MD 1.4 lower (7.54 lower to 4.74 higher)	-	82 (2 RCTs)	⊕⊝⊝⊝ VERY LOW a b c
Depression assessed with: Beck Depression Inventory Lower score = better	The mean score with no treatment ranged from 10.5 to 11.7	MD 3.8 lower (6.9 lower to 0.69 lower)	-	82 (2 RCTs)	⊕⊝⊝⊝ VERY LOW a b c
Anxiety (state) assessed with: State sub-score of the state-trait inventory Lower score = better	The mean score with no treatment ranged from 42.2 to 44.5	MD 8.63 lower (12.48 lower to 4.77 lower)	-	82 (2 RCTs)	⊕⊝⊝⊝ VERY LOW a b c
Anxiety (trait) assessed with: Trait sub-score of the state-trait inventory Lower score = better	The mean score with no treatment ranged from 46.5 to 48.5	MD 3.98 lower (7.96 lower to 0)	-	82 (2 RCTs)	⊕⊝⊝⊝ VERY LOW a b d

*__The risk in the intervention group__ (and its 95% confidence interval) is based on the assumed risk in the comparison group and the __relative effect__ of the intervention (and its 95% CI).

CI: Confidence interval; **RR:** Risk ratio; **MD** mean difference; **RCT:** randomized controlled trial

GRADE Working Group grades of evidence
High certainty: We are very confident that the true effect lies close to that of the estimate of the effect
Moderate certainty: We are moderately confident in the effect estimate: The true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different
Low certainty: Our confidence in the effect estimate is limited: The true effect may be substantially different from the estimate of the effect
Very low certainty: We have very little confidence in the effect estimate: The true effect is likely to be substantially different from the estimate of effect

[a] Downgraded one level for study limitations: lack of blinding and poor reporting on key risk of bias domains lead us to consider a high risk of bias for all trials.
[b] Downgraded one level for indirectness: this review was on whether biofeedback is safe and effective for IBS, yet these meta-analyzed trials test a complex intervention which includes biofeedback as well as other interventions.
[c] Downgraded one level for imprecision: the 95% confidence interval is wide and includes both a small and large effect.
[d] Downgraded one level for imprecision: the 95% confidence interval is wide and includes both a no effect and a large effect.

Summary of findings 6. Multi-component psychological intervention (with biofeedback) compared to attention control for irritable bowel syndrome

Multi-component psychological intervention (with biofeedback) compared to attention control for irritable bowel syndrome

Patient or population: people with irritable bowel syndrome
Setting: outpatient setting
Intervention: multi-component psychological intervention (with biofeedback)
Comparison: attention control

Outcomes	Anticipated absolute effects* (95% CI)		Relative effect (95% CI)	№ of participants (studies)	Certainty of the evidence (GRADE)	Comments
	Risk with attention control	Risk with multi-component psychological intervention (with biofeedback)				
Composite Primary Symptom Reduction Score (CPSR) Scale from: 0% to 100% Higher score = better follow-up: 8 weeks	The mean score with attention control ranged from 30.2 to 38.0	MD 4.02 higher (21.41 lower to 29.45 higher)	-	80 (2 RCTs)	⊕⊖⊖⊖ VERY LOW a b c	
Clinical response assessed with: 50% improvement in composite symptom score	Study population		RR 1.10 (0.72 to 1.69)	80 (2 RCTs)	⊕⊖⊖⊖ VERY LOW a b c	
	487 per 1,000	536 per 1,000 (351 to 823)				
Quality of life (QoL)	No formal quality of life scales were used in the included trials.		-	-	-	
Adverse events (AE)	Adverse events were not reported in these studies.		-	-	-	
Serious adverse events (SAE)	Serious adverse events were not reported in these studies.		-	-	-	
Abdominal Pain (Pain) assessed with: symptom diaries Lower score=better follow-up: 8 weeks	The mean score with attention control ranged from 11.7 to 13.5	MD 0.72 higher (5.4 lower to 6.84 higher)	-	80 (2 RCTs)	⊕⊖⊖⊖ VERY LOW a b c	
Depression assessed with: Beck Depression Inventory Lower score = better	The mean score with attention control ranged from 6.7 to 7.9	MD 0.13 higher (2.73 lower to 2.98 higher)	-	80 (2 RCTs)	⊕⊖⊖⊖ VERY LOW a b c	

Anxiety (state) assessed with: State sub-score of the state-trait inventory Lower score = better	The mean score with attention control ranged from 36.2 to 36.3	MD 0.74 lower (5.38 lower to 3.89 higher)	-	80 (2 RCTs)	⊕⊖⊖⊖ VERY LOW a b c
Anxiety (trait) assessed with: Trait sub-score of the state-trait inventory Lower score = better	The mean score with attention control ranged from 39.6 to 40.8	MD 2.05 higher (2.48 lower to 6.57 higher)	-	80 (2 RCTs)	⊕⊖⊖⊖ VERY LOW a b c

*__The risk in the intervention group__ (and its 95% confidence interval) is based on the assumed risk in the comparison group and the __relative effect__ of the intervention (and its 95% CI).

CI: Confidence interval; **RR:** Risk ratio; **MD:** mean difference; **RCT:** randomized controlled trial

GRADE Working Group grades of evidence
High certainty: We are very confident that the true effect lies close to that of the estimate of the effect
Moderate certainty: We are moderately confident in the effect estimate: The true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different
Low certainty: Our confidence in the effect estimate is limited: The true effect may be substantially different from the estimate of the effect
Very low certainty: We have very little confidence in the effect estimate: The true effect is likely to be substantially different from the estimate of effect

[a] Downgraded one level for imprecision: the 95% confidence interval includes both no effect and effect.
[b] Downgraded one level for study limitations: lack of blinding and poor reporting on key RoB domains lead us to consider a high risk of bias for both trials.
[c] Downgraded one level for indirectness: this review was on whether biofeedback is safe and effective for IBS, yet these meta-analyzed trials test a complex intervention which includes biofeedback as well as other interventions.

Summary of findings 7. Biofeedback compared to relaxation training for irritable bowel syndrome

Biofeedback compared to relaxation training for irritable bowel syndrome

Patient or population: people with irritable bowel syndrome
Setting: outpatient setting
Intervention: biofeedback
Comparison: relaxation training

Outcomes	Anticipated absolute effects* (95% CI)		Relative effect (95% CI)	№ of participants (studies)	Certainty of the evidence (GRADE)	Comments
	Risk with relaxation training	Risk with biofeedback				

Clinical improvement assessed with: severity of symptoms (measurement scale used unclear) Lower score = better	The mean severity of symptoms in the biofeedback group was 3.20 at pretest and 2.80 post-test. The relaxation control group mean severity was 3.50 pretest and 2.50 post-test. .	-	10 (1 RCT)	⊕⊖⊖⊖ VERY LOW [a b c]
Quality of life (QoL)	No formal quality of life scales were used in the trial.	-	-	-
Adverse events (AE)	Adverse events were not reported in this study.	-	-	-
Serious adverse events (SAE)	Serious adverse events were not reported in this study.	-	-	-
Stool Frequency assessed with: diary	Stool frequency was measured using patient diaries and a decrease in stool frequency was reported in all study arms but outcome level data for between group differences were not reported.	-	10 (1 RCT)	⊕⊖⊖⊖ VERY LOW [d]
Abdominal pain (Pain) assessed with: self report	There was no difference between groups in abdominal pain (only statistical tests, not summary effect sizes were provided).	-	10 (1 RCT)	⊕⊖⊖⊖ VERY LOW [d]
Depression assessed with: HCL 90-R	Scores from a depression subcategory of the HCL 90-R were reported. All groups had an improvement from baseline to post-treatment but that the between group comparisons were similar (P=0.60) (group level effect sizes and within group P values were not provided).	-	10 (1 RCT)	⊕⊖⊖⊖ VERY LOW [d]
Anxiety assessed with: HCL 90-R	Scores from an anxiety subcategory of the HCL 90-R were reported. All groups had improvement pre/post-treatment (P < 0.007) but the between group comparisons were equivalent (group level effect sizes and specific between and within group P values were not provided).	-	10 (1 RCT)	⊕⊖⊖⊖ VERY LOW [d]

*__The risk in the intervention group__ (and its 95% confidence interval) is based on the assumed risk in the comparison group and the __relative effect__ of the intervention (and its 95% CI).

__RCT:__ randomized controlled trial

GRADE Working Group grades of evidence
High certainty: We are very confident that the true effect lies close to that of the estimate of the effect
Moderate certainty: We are moderately confident in the effect estimate: The true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different
Low certainty: Our confidence in the effect estimate is limited: The true effect may be substantially different from the estimate of the effect
Very low certainty: We have very little confidence in the effect estimate: The true effect is likely to be substantially different from the estimate of effect

[a] Downgraded one level for study limitations: high risk of bias study.
[b] Downgraded one level for imprecision: SD were not reported. The between group difference was small.
[c] Downgraded an additional level for study limitations: measures of variation and statistical significance were not reported.
[d] Downgraded two levels for study limitations (the study was at high risk of bias and the outcome was incompletely reported), and one level for serious imprecision (small sample size).

BACKGROUND

Description of the condition

Irritable bowel syndrome (IBS) is a common disorder which affects an estimated 11% of individuals worldwide (Canavan 2014). Its definition and diagnostic criteria have varied over the years, with the most current version released by an international group of experts in 2016 as Rome IV (Drossman 2016). In short, IBS is a functional bowel disorder marked by chronic and recurrent abdominal pain which improves with defecation, or worsens in tandem with changes in stool frequency or consistency. IBS is commonly divided into subtypes: diarrhea predominant (IBS-D), constipation predominant (IBS-C), mixed (IBS-M), and unsubtyped (IBS-U) (Drossman 2016).

Clinicians often have difficulty achieving satisfactory control of IBS symptoms. Pharmacologic treatments tend to be aimed at symptom control, and effective therapies that obtain or prolong remission of symptoms are elusive (Halland 2015). These options cross multiple categories of medication, and are often prescribed based on the subtypes of the condition (Rao 2015). Multiple psychological interventions have been given to people with IBS, with varying degrees of success (Zijdenbos 2009).

We currently lack comprehensive data about the impact of IBS on total healthcare expenditures. A review of over 3000 people with IBS-C in the United States, compared to non-IBS controls, concluded that the healthcare costs totaled 3856 US dollars (USD) per patient per year (Doshi 2014). In China, direct annual patient costs related to IBS are an estimated USD 763 per year (Fan 2017).

Description of the intervention

Biofeedback is "a process that enables an individual to learn how to change physiological activity for the purposes of improving health and performance" (AAPB 2016). Biofeedback sessions include real-time monitoring of an individual's physiological signals, which are then displayed back to the individual. Examples of such signals include temperature fluctuations, skin conductance, heart rate variability, muscle activity, and respiration patterns. In clinical and educational settings, biofeedback is mostly conducted using computerized models that use graphs, images and sounds to give feedback on these signals to the person. The goal of biofeedback is to use this feedback to help an individual develop self-awareness of their physiological states. In theory, this awareness may lead to better control over autonomic activity, and improved health outcomes (Peper 2009).

One illustrative example of biofeedback in a clinical setting would be the use of a clip-on ear lobe probe that measures heart rate variability during a relaxing meditation session. The goal of this type of exercise would be to help a person recognize and reproduce a relaxed state during times of stress (Wheat 2010).

How the intervention might work

The etiology of IBS is still not fully elucidated, and may incorporate multiple domains, including colonic dysmotility, visceral hypersensitivity, immunologic, microbiotic, and dietary factors, as well as elements of brain-gut interaction (Lee 2014). In regards to the latter, researchers have identified a disturbance in sympatho-vagal balance in IBS sufferers when compared to controls (Pellissier 2010; Sowder 2010).

The autonomic nervous system is comprised of three branches, including the sympathetic, parasympathetic and enteric nervous systems. Through these three divisions, the autonomic nervous system influences gastrointestinal motility, secretion and immune function (Elenkov 2000; Hansen 2003). Increased sympathetic and reduced parasympathetic nervous system activity is the most common pattern observed in people with IBS, when compared to controls (Manabe 2009).

Modulation of the autonomic nervous system, to favor increased sympathetic and reduced parasympathetic activity, is a key component of the stress response. Subsequent changes in gastrointestinal function that result from this pattern of stress modulation are one potential mechanism underlying IBS symptoms (Manabe 2009).

Biofeedback has been proposed to help users gain some control over physiologic processes, including sympatho-vagal balance (e.g. autonomic nervous system function). Research in other functional bowel disorders (e.g. functional abdominal pain) has demonstrated that biofeedback can improve sympatho-vagal balance and disease symptomatology (Sowder 2010). Biofeedback interventions have been studied in other gastrointestinal conditions. For instance, biofeedback has been used to manage functional constipation (Woodward 2014), and fecal incontinence (Norton 2012). Many functional bowel disorders have overlapping symptomatology, and in some instances are beginning to be viewed as different ends of a continuum of symptom presentations (Drossman 2016). Considering the positive, though preliminary, evidence for the benefit of biofeedback in other gastrointestinal conditions with symptoms which overlap that of IBS, we wished to investigate the efficacy of biofeedback interventions in IBS.

Why it is important to do this review

Irritable bowel syndrome is a common functional bowel disorder that is associated with impaired quality of life and increased healthcare costs, but which lacks reliable treatment options (Lee 2014). Biofeedback-based interventions are a group of low risk interventions that have been shown to be potentially effective in IBS (Dobbin 2014). To our knowledge, the available randomized trial evidence on using biofeedback for IBS has not previously been systematically reviewed.

OBJECTIVES

Our primary objective was to assess the efficacy and safety of biofeedback-based interventions for IBS in adults and children.

METHODS

Criteria for considering studies for this review

Types of studies

We included randomized controlled trials (RCTs) of biofeedback treatment for IBS. We included studies that used active treatment, no treatment, sham treatment, or placebo as a control. We did not apply any language restrictions, and included studies published either as abstracts or full papers.

Types of participants

Our inclusion criteria specified that participants should be adults or children diagnosed with IBS, as defined by the trial authors. As

the diagnostic criteria for IBS have changed over time (Drossman 2016), we chose to be as inclusive as possible to minimize selection bias. However, differing diagnostic criteria was one of our a priori subgroups to explore potential heterogeneity (see Subgroup analysis and investigation of heterogeneity).

Types of interventions

We included trials investigating all forms of biofeedback. If the trial authors had not explicitly described an intervention as biofeedback, we used the Association for Applied Psychophysiology and Biofeedback's (AAPB) definition of biofeedback to guide eligibility decisions (AAPB 2016).

This definition describes biofeedback as, "a process that enables an individual to learn how to change physiological activity for the purposes of improving health and performance. Precise instruments measure physiological activity such as brainwaves, heart function, breathing, muscle activity, and skin temperature. These instruments rapidly and accurately 'feed back' information to the user. The presentation of this information — often in conjunction with changes in thinking, emotions, and behavior — supports desired physiological changes. Over time, these changes can endure without continued use of an instrument" (AAPB 2016).

We also included studies that used other treatment modalities in addition to biofeedback (e.g. progressive muscle relaxation). We did not, however, pool these studies with biofeedback-only trials. Some of these studies used relaxation training techniques without biofeedback as the control group in their research methodology. We used the term 'attention control' to represent 'relaxation training without biofeedback' throughout the review.

Types of outcome measures

Primary outcomes

- Global or clinical improvement, as defined by the included studies (e.g. IBS Severity Scoring System [IBS-SSS], or the Gastrointestinal Symptom Rating Scale [GSRS])
- Quality of life (e.g. overall well-being, Irritable Bowel Syndrome Quality of Life questionnaire [IBS-QoL], Short Form Health Survey [SF-36])

Secondary outcomes

- Adverse events (if available, using the National Institute for Health (NIH) Common Terminology Criteria for Adverse Events version 4.0)
- Withdrawal due to adverse events
- Serious adverse events
- Stool frequency
- Stool consistency (e.g. as rated by the Bristol Stool Scale)
- IBS-C stool frequency weekly responder (defined as a participant who experiences an increase of at least one complete spontaneous bowel movement per week from baseline; FDA 2012; MacDougall 2013.)
- IBS-D stool frequency weekly responder (defined as a 50% or more reduction in the number of days per week with at least one stool that has a Bristol consistency score of type 6 or 7, compared with baseline; FDA 2012.)
- Improvement in abdominal pain frequency and severity
- Depression (e.g. Beck Depression Inventory)
- Anxiety (e.g. State-Trait Anxiety Inventory)

Search methods for identification of studies

Electronic searches

We searched the following databases from inception to 24 July 2019:

- the Cochrane Inflammatory Bowel Disease (IBD) Group Specialized Register;
- the Cochrane Central Register of Controlled Trials (CENTRAL);
- MEDLINE;
- Embase;
- the Cumulative Index to Nursing and Allied Health Literature (CINAHL); and
- the Allied and Complementary Medicine Database (AMED).

We customized the search strategies for each database and used the recommended Cochrane search string for the identification of RCTs. We did not apply any language restrictions. Appendix 1 reports the search strategies.

Searching other resources

We searched for additional, ongoing and unpublished studies through the following additional resources, including the grey literature:

- reference lists of included studies, and those of any relevant systematic reviews identified;
- clinical trial registries: ClinicalTrials.gov (clinicaltrials.gov), ICTRP (www.who.int/ictrp/en/) and ISRCTN Registry (www.isrctn.com/);
- contacting biofeedback device manufacturers, researchers and practitioners to determine knowledge of ongoing or unpublished trials;
- searching for published abstracts from conference proceedings: Biosis Citation Index, Scopus, Web of Science;
- reviewing theses and dissertations in ProQuest Dissertations & Theses Global; and
- searching open Access Journals: Directory of Open Access Journals and Highwire Press.

Data collection and analysis

Selection of studies

A research librarian (JB) conducted the search and compiled identified papers into a citation manager. Four of the authors (JG, MB, MH, RB) worked in pairs, independently and in duplicate, to review these citations for inclusion, based on the criteria described in Criteria for considering studies for this review. First, they screened at the title level, then they reviewed the included papers at the abstract level. Finally, they reviewed the full text of the remaining papers against the inclusion criteria, using a standardized inclusion form. Throughout the process, the review authors resolved disagreements by consensus. At all stages, the review authors noted the reasons for exclusion. We asked a translator to assess any non-English language papers. To limit selection bias, we also included studies that were published as abstract only. We attempted to contact the abstracts' authors for further details, including final results.

Data extraction and management

Two authors (JG, MB) extracted data from the Included papers independently and in duplicate, and resolved any disagreements by consensus. They used a standardized extraction form to collect the following information:

- author;
- year of publication;
- language;
- study setting (country, inpatient, outpatient);
- funding source;
- inclusion and exclusion criteria for participants;
- participant characteristics (age, gender, diagnosis, socioeconomic status);
- number of participants randomized to each group;
- presence or absence of intention-to-treat analysis (whether participants for whom data were available were analyzed as randomized);
- participants lost to follow-up (LTFU), with reasons for LTFU described, and information about any methods of imputation used within the primary analysis;
- measures of compliance;
- type of biofeedback used;
- duration and frequency of biofeedback;
- duration of study period;
- duration of follow-up;
- co-interventions;
- disease severity at baseline;
- primary and secondary outcomes, as defined by study authors;
- outcome instruments used;
- symptoms (e.g. pain, bloating);
- quality of life (e.g. overall well-being, IBS-QoL);
- adverse events (using NIH Common Terminology Criteria for Adverse Events version 4.0 ideally, but per author definition if common terminology criteria were not available);
- stool frequency;
- stool consistency (e.g. Bristol Stool Scale);
- IBS-C stool frequency weekly responder (defined as a participant who experiences an increase of at least one complete spontaneous bowel movement per week from baseline);
- IBS-D predominant stool frequency weekly responder (defined as a 50% or more reduction in the number of days per week with at least one stool that has a consistency of type 6 or 7 compared with baseline);
- improvement in abdominal pain frequency and severity;
- depression; and
- anxiety.

We attempted to contact all trial researchers to clarify missing data, or to ask for relevant unpublished data. We made attempts to contact first, corresponding, and senior authors.

Assessment of risk of bias in included studies

We evaluated each of the included studies with the Cochrane 'Risk of bias' tool, to assess sequence generation, allocation concealment, blinding of participants and personnel, blinding of outcome assessment, incomplete outcome data, selective outcome reporting, and other sources of bias (Hartling 2009; Higgins 2011). Two authors (JG, MB) reviewed the studies independently and in duplicate, and resolved any disagreement by consensus. If we were unable to clarify missing risk of bias domains, we assessed studies as having an unclear risk of bias.

We know from well-conducted placebo studies on IBS that elaborate placebo comparisons can yield very high non-specific (placebo) effects (Kaptchuk 2008). We also know from this work that the magnitude of non-specific effects can be substantial and vary depending upon the level of elaborateness, physician interaction, ritual etc. Because IBS can have such a large placebo response and the magnitude of that response depends substantially on the level of elaborateness of the control (the extent of which is not always clear in published work), we adopted the following decision making process in evaluating our trials for risk of performance bias.

- Biofeedback versus no-treatment control was assessed as high risk of bias
- Biofeedback versus active control was assessed as unclear risk of bias
- Biofeedback versus attention control was assessed as unclear risk of bias

We also employed the GRADE system for rating overall certainty of evidence. In particular, randomized trials begin as high quality evidence, but may be rated down by one or more of five categories of limitations: (1) risk of bias, (2) consistency, (3) directness, (4) imprecision, and (5) reporting bias. The certainty of evidence for each main outcome can be determined after considering each of these elements, and categorized as either high (we are very confident that the true effect lies close to that of the estimate of the effect); moderate (we are moderately confident in the effect estimate: the true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different); low (our confidence in the effect estimate is limited: the true effect may be substantially different from the estimate of the effect); very low (we have very little confidence in the effect estimate: the true effect is likely to be substantially different from the estimate of effect) (Guyatt 2008).

Measures of treatment effect

We presented dichotomous data as risk ratios (RR), and continuous data as mean differences (MD), with corresponding 95% confidence intervals (CI). Using control event risks from the included trials, we calculated the number needed to treat for an additional beneficial outcome (NNTB) or the number needed to treat for an additional harmful outcome (NNTH).

Unit of analysis issues

To avoid unit of analysis issues, we chose the first intervention phase of any identified cross-over study for our analysis. Likewise, for multiple intervention arm trials, we planned to split the control group in order to avoid unit of analysis issues. Finally, for studies with repeated observations on trial participants, we only used one data point from the participant. For example, if a trial reported multiple adverse events per participant, we used the total number of participants with adverse events for our analysis, rather than the total number of adverse events.

Dealing with missing data

We noted information about missing outcome data at the data extraction stage. We considered trials that had 10% or more missing outcome data to have a high risk of bias for the attrition domain of the Cochrane 'Risk of bias' tool. In line with recent recommendations, we used a complete case analysis for our primary analysis, but when relevant, we carried out a sensitivity analysis to assess the potential influence of missing outcome data on our primary outcomes (Guyatt 2017; Akl 2015; Ebrahim 2013). For these sensitivity analyses, we elected to make assumptions about the missing data that were extreme but also plausible. For example, for the dichotomous outcome of adverse events, we would assume that the missing participants in the control group had adverse events at the same rate as those analyzed, while for the biofeedback group we would assume that their missing participants had adverse events at rates of 1.5:1, 2:1, 3:1, and 5:1 of those analyzed. We would then ascertain if the effect estimate survived the extreme plausible assumptions (Guyatt 2017; Akl 2015; Ebrahim 2013).

When trials did not report standard deviations (SD) and we were unable to contact the authors, we estimated the SD from the t value, if available, as per the *Cochrane Handbook* (Section 7.7.3).

Assessment of heterogeneity

Heterogeneity in systematic reviews is generally described as clinical, methodological, and statistical (Deeks 2011). The former two may or may not be reflected within formal tests for statistical heterogeneity, but may still be present and important to investigate (Gagnier 2013). We therefore followed the proposed 13 recommendations for assessing and investigating clinical heterogeneity in systematic reviews (Gagnier 2013). Appendix 2 describes this approach.

Statistical heterogeneity was investigated using the I^2 statistic using the following thresholds as a guide, as per the *Cochrane Handbook for Systematic Reviews of Interventions*: 0% to 40% might not be important; 30% to 60% may represent moderate heterogeneity; 50% to 90% may represent substantial heterogeneity; and 75% to 100% may indicate considerable heterogeneity (Deeks 2011).

Assessment of reporting biases

We attempted to identify protocols of included trials via trial registries (e.g. ClinicalTrials.gov). If found, we planned to compare protocols with published papers to look for reporting biases. To evaluate the potential for publication bias and other small study effects, we were to follow published guidelines and inspect the funnel plots of each outcome for visual evidence of asymmetry and, when appropriate, conduct Harbord's linear regression test to investigate statistical evidence of small study effects (Harbord 2006; Sterne 2011). As per the guidelines, we did not conduct a funnel plot, as there were fewer than 10 trials included in the meta-analysis (Sterne 2011).

Data synthesis

We combined data in a meta-analysis using a fixed-effect model for the primary analysis, and conducted a sensitivity analysis using a random-effects model. We used a fixed-effect model because the only trials that could be combined used identical interventions. We also considered a fixed-effect model to be appropriate given the limitations of estimating between-study heterogeneity with so few studies.

Subgroup analysis and investigation of heterogeneity

Investigation of heterogeneity, including using subgroup analyses, is described in Appendix 2. In short, the consensus recommendations for heterogeneity investigation as per the 2013 heterogeneity Delphi group findings were followed (Gagnier 2013). In addition, we planned to subject all subgroup analyses to a credibility checklist, as proposed by Sun and colleagues (Sun 2012).

Sensitivity analysis

We conducted both fixed-effect and random-effects meta-analyses. Additionally, we followed the GRADE guidance on handling missing participant outcome data (Guyatt 2017). That is, when pooled estimates were statistically significant, we imputed outcome data that were missing, to challenge the robustness of the pooled estimates (Guyatt 2017). For dichotomous outcomes, we assumed that the missing participants in the control group had a clinical response at the same rate as those successfully followed, while for the biofeedback group we assumed their missing participants had a clinical response at progressively worse rates when compared to those successfully followed. For continuous outcomes, we imputed means for missing outcome data assuming increasingly strict assumptions and, as recommended, used the median SD of the control group of the included trials for variability of the imputed data. Unlike the best-case, worst-case scenario, the assumptions are plausible but not extreme.

RESULTS

Description of studies

Results of the search

The primary literature search identified 1497 records, with the grey literature search identifying an additional 3542 records. After removal of duplicates, we screened 4353 records and selected 167 full text articles for further review. Of these, eight trials (in seven publications) met our inclusion criteria and we included these in our qualitative synthesis. The studies by Blanchard 1992a and Blanchard 1992b were two separate studies reported within a single publication. Four outcomes (clinical response, abdominal pain, depression, and anxiety) had trials with sufficiently homogenous treatment and outcome measures to allow for meta-analysis for two comparisons (active versus no-treatment control and active versus attention control).

We included three studies in the qualitative synthesis for the comparison 'active versus no-treatment control' (Blanchard 1992a; Blanchard 1992b; Neff 1987), and two studies for the quantitative synthesis of 'active versus attention control' (Blanchard 1992a; Blanchard 1992b). See Figure 1 for the PRISMA study flow diagram.

Figure 1. PRISMA study flow diagram.

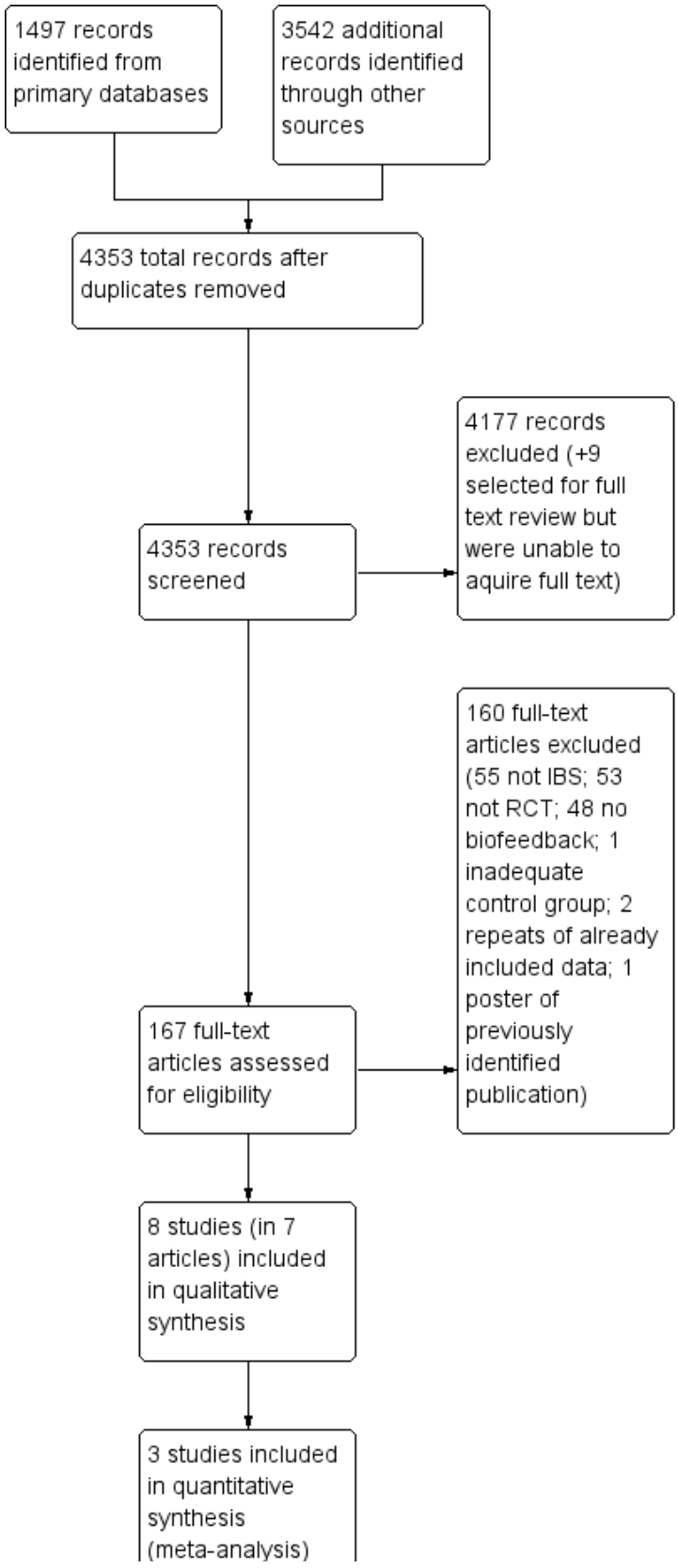
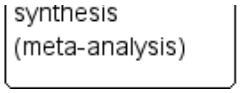


Figure 1. (Continued)



Included studies

We have summarized the key characteristics of the included studies below, with further details in the Characteristics of included studies table.

Design

All included trials were randomized controlled trials as per our inclusion criteria. Four trials used three arms (Blanchard 1992a; Blanchard 1992b; DeRoo 1988; Trembach 2009), the remaining trials were two armed trials.

The Characteristics of included studies table gives further details about study design.

Sample sizes

The included studies ranged in size from 13 to 92 participants. There was a total of 300 subjects across the eight included trials.

Setting

All trials were in an outpatient setting and enrolled community-dwelling individuals.

Participants

All trials enrolled adults only. All of the trials exclusively enrolled participants with irritable bowel syndrome. One study enrolled people with IBS-D only (DeRoo 1988), one study enrolled people with IBC-C only (Trembach 2009), no studies exclusively enrolled people with IBS-M, and the remaining six studies were not exclusive to a single IBS subtype. Two studies exclusively enrolled women (Dobbin 2013; Trembach 2009). The diagnostic criteria used to determine IBS diagnosis were heterogeneous, but each trial required that a medical professional should have made the diagnosis.

Interventions

The type and duration of biofeedback intervention varied from trial to trial. Interventions included multi-component interventions, such as including progressive muscle relaxation (e.g. Blanchard 1992a), as well as exclusively biofeedback intervention arms (e.g. Thompson 2010). The Characteristics of included studies table gives further details of the types of biofeedback interventions.

Comparators

Comparators varied among trials and included active controls (e.g. Dobbin 2013), attention controls (e.g. Blanchard 1992a), wait-list controls (e.g. Blanchard 1992b), and sham biofeedback controls (e.g. DeRoo 1988). The Characteristics of included studies table summarizes the details about comparators.

Outcomes

Outcome measures exhibited significant heterogeneity and included the IBS-SSS (Dobbin 2013) and the IBS impact scale (Thompson 2010) among many others. Of the outcomes used, only the composite primary symptom reduction score (CPSR) was used by multiple studies, Four trials used the CPSR (Blanchard 1992a; Blanchard 1992b, Neff 1987; Thompson 2010). The Characteristics of included studies table gives further details of each trial's outcome assessment.

Funding Sources

None of the included studies reported funding sources clearly.

Excluded studies

We excluded 4177 records at the title and abstract stage of study selection. We were unable to acquire the full text of nine studies that we had selected for further review, despite considerable effort by the review authors and supplementary librarian support. Of the 167 full text studies reviewed, we excluded 160 for the following reasons: 55 not IBS, 53 not RCT, 48 not biofeedback, 1 inadequate control group, 2 were duplicate reports of already included studies, and 1 a poster of a previously identified publication. The 'Characteristics of excluded studies' table gives some examples of excluded studies.

Risk of bias in included studies

We considered the overall risk of bias to be high or unclear in all included trials, primarily with respect to blinding (Figure 2; Figure 3). We describe below the risk of bias by domain, and give further details in the Characteristics of included studies table.

Figure 2. Risk of bias graph: review authors' judgements about each risk of bias item presented as percentages across all included studies.

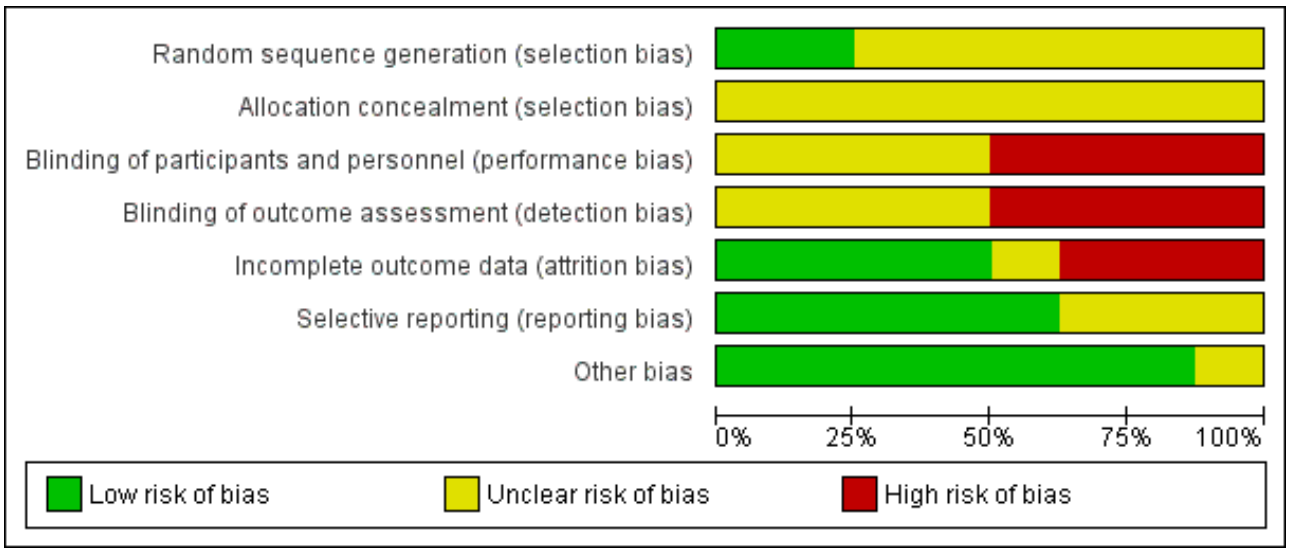
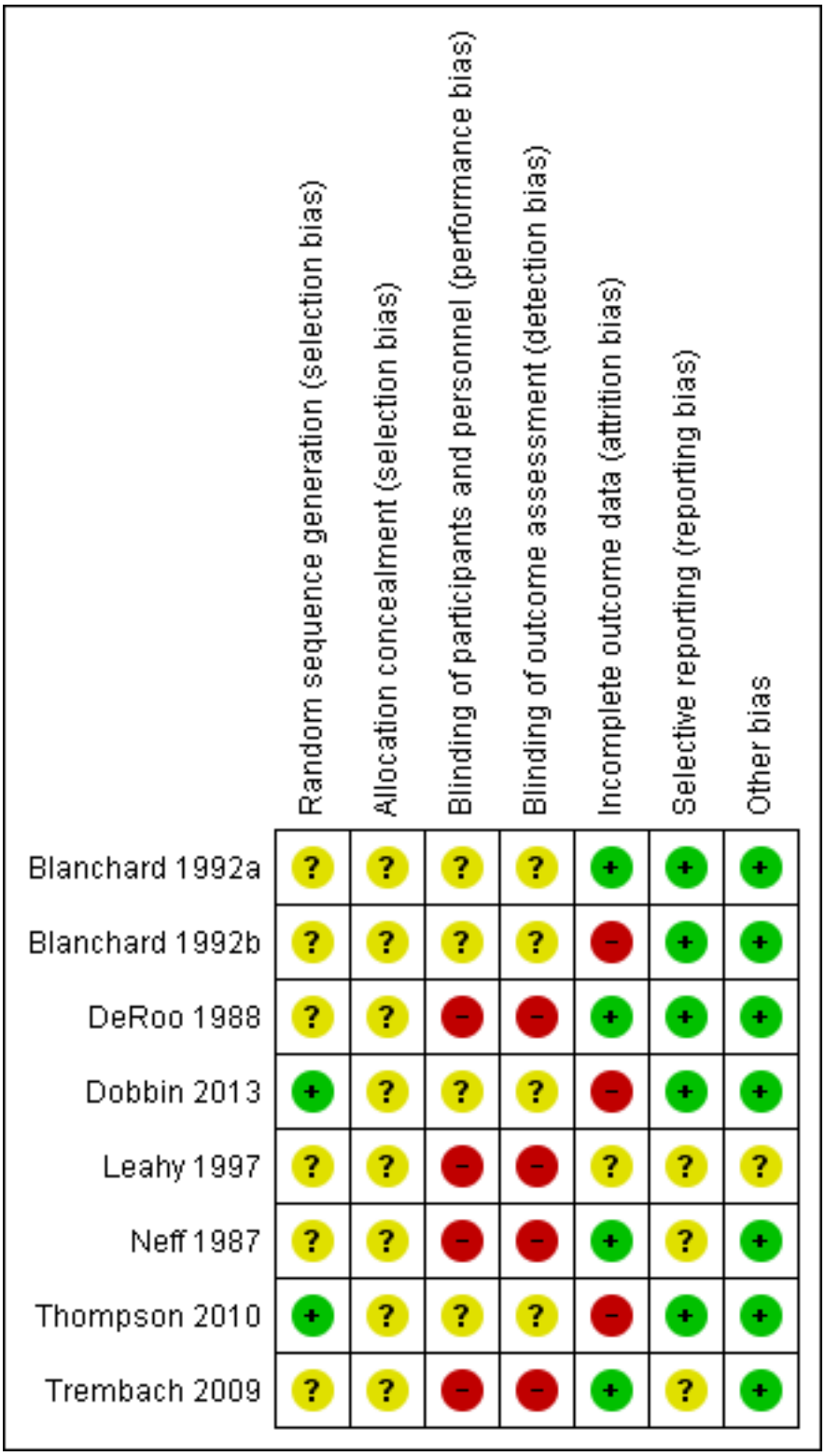


Figure 3. Risk of bias summary: review authors' judgements about each risk of bias item for each included study.



Allocation

Only two included trials described the randomization process, and we judged these to have a low risk of bias (Dobbin 2013; Thompson 2010). The others did not describe this process, and we judged these to have an unclear risk of bias. Similarly, none of the included papers described allocation concealment, so we judged them all to have an unclear risk of bias.

Blinding

Four of the included trials were clearly unblinded, so we judged these to have a high risk of bias in both blinding domains (performance bias and detection bias) (DeRoo 1988; Leahy 1997; Neff 1987; Trembach 2009). In the other four trials, it was unclear whether participants and personal were blind to which of the active groups was the group of interest, so we judged these to have an unclear risk of bias (Blanchard 1992a; Blanchard 1992b; Dobbin 2013; Thompson 2010).

Incomplete outcome data

Using our a priori cut-off of 10% dropouts as a rationale for a high risk of attrition bias, we judged one of our included studies to have a high risk of bias in this domain (Blanchard 1992b). One trial did not include information on dropouts, so we judged this to have an unclear risk of bias (Leahy 1997). The other six trials had fewer than 10% dropouts, so we judged them to be at low risk of attrition bias (Blanchard 1992a; DeRoo 1988; Dobbin 2013; Neff 1987; Thompson 2010; Trembach 2009).

Selective reporting

One of our included trials (Neff 1987) used a composite score that was different from the outcome measure used in a pilot trial by the same research team. We judged this to be suspicious for selective outcome reporting bias. Two of the other trials did not include sufficient information about how the scales were developed or whether any further data were collected, so we rated these as an unclear risk of bias (Leahy 1997; Trembach 2009). We judged the other five trials to have a low risk of bias in this domain (Blanchard 1992a; Blanchard 1992b; DeRoo 1988; Dobbin 2013; Thompson 2010).

Other potential sources of bias

One trial was reported as an abstract only, and we were unsuccessful in making follow-up contact with the authors (Leahy 1997). We therefore judged this to have an unclear risk of bias in this domain. We did not consider that the other trials had important risk of bias issues with respect to baseline distribution, stopping early for benefit, or any other undefined reason. We therefore judged these to be at low risk of other bias.

Effects of interventions

See: **Summary of findings for the main comparison** Biofeedback plus standard therapy compared to standard therapy for irritable bowel syndrome; **Summary of findings 2** Biofeedback plus standard therapy compared to sham biofeedback plus standard therapy for irritable bowel syndrome; **Summary of findings 3** Biofeedback compared to hypnotherapy for irritable bowel syndrome; **Summary of findings 4** Biofeedback compared to counseling for irritable bowel syndrome; **Summary of findings 5** Multi-component psychological intervention (with biofeedback) compared to no-treatment control for irritable bowel syndrome; **Summary of findings 6** Multi-component psychological intervention (with biofeedback) compared to attention control for irritable bowel syndrome; **Summary of findings 7** Biofeedback compared to relaxation training for irritable bowel syndrome

The included trials evaluated the effects of biofeedback for IBS across seven comparisons. The summary of findings tables for clinical improvement, quality of life, adverse events, serious adverse events, abdominal pain, depression, and anxiety for each comparison can be found: Summary of findings for the main comparison (Biofeedback plus standard therapy versus standard therapy), Summary of findings 2 (Biofeedback plus standard therapy versus sham biofeedback versus standard therapy), Summary of findings 3 (Biofeedback versus hypnotherapy), Summary of findings 4 (Biofeedback versus counseling), Summary of findings 5 (Multi-component psychological intervention (with biofeedback) versus no-treatment control), Summary of findings 6 (Multi-component psychological intervention (with biofeedback) versus attention control), Summary of findings 7 (Biofeedback versus relaxation training). We have reviewed the results of these comparisons by outcome below.

Primary outcomes

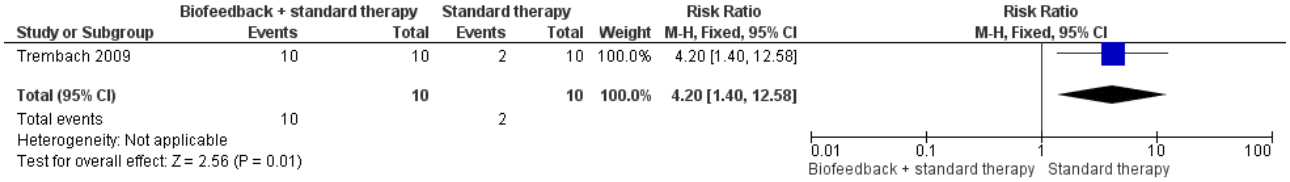
Global or clinical improvement

The included studies used numerous measures of global or clinical improvement. They are delineated below, organized by comparison.

Biofeedback plus standard therapy versus standard therapy

Trembach 2009 reported on clinical improvement by stratifying the participants' six month results by no improvement, inadequate improvement, significant improvement, and remission. One hundred per cent (10/10) of participants reached adequate improvement or remission with standard therapy (fiber and medication) plus biofeedback at six months compared to 20% (2/10) of the participants receiving standard therapy alone (RR 4.20, 95% CI 1.40 to 12.58; n = 20; P = 0.01; NNTB = 1, very low-certainty evidence) (Figure 4; Analysis 1.1)

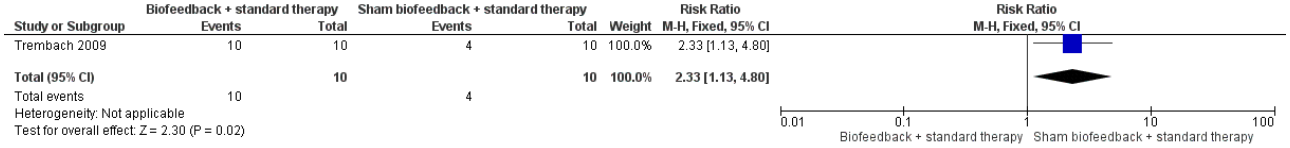
Figure 4. Forest plot of comparison: 1 Biofeedback plus Standard Therapy versus Standard Therapy, outcome: 1.1 Clinical Response.



Biofeedback plus standard therapy versus sham biofeedback plus standard therapy

Trembach 2009 reported on clinical improvement by stratifying the participants' six month results by no improvement, inadequate improvement, significant improvement, and remission. One hundred per cent (10/10) of participants reached adequate improvement or remission with standard therapy (fiber and medication) plus biofeedback at six months compared to 40% (4/10) of participants receiving standard therapy plus sham biofeedback (RR 2.33, 95% CI 1.13 to 4.80, n = 20; P = 0.02; NNTB = 2; very low-certainty evidence) (Figure 5; Analysis 2.1).

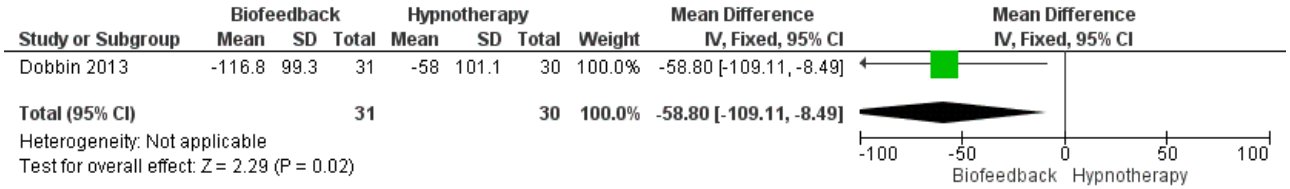
Figure 5. Forest plot of comparison: 2 Biofeedback plus Standard Therapy versus Sham Biofeedback plus Standard Therapy, outcome: 2.1 Clinical Response.



Biofeedback versus hypnotherapy

Using the 500 point IBS-SSS, Dobbin 2013 reported a 58.8 point difference in favor of heart rate variability biofeedback, between the biofeedback group and the hypnotherapy active control at 12 weeks (MD -58.80, 95% CI -109.11 to -8.49; n = 61; P = 0.02; low-certainty evidence) (Figure 6; Analysis 3.1).

Figure 6. Forest plot of comparison: 3 Biofeedback versus Hypnotherapy, outcome: 3.1 Symptom Improvement (measured by IBS-SSS).



Biofeedback versus counseling

Thompson 2010 used heart rate variability biofeedback as a single intervention compared to a cognitive therapy active control in their eight-week, two-armed trial (29 participants). They also used the CPSR as a measure of clinical improvement. They reported a greater improvement in the biofeedback group (mean = 38.5) compared to the cognitive therapy group (mean = 31.5), but the difference was small and the effect of chance cannot be ruled out (MD 7.03, 95% CI -51.07 to 65.13; n = 29, P = 0.81, low-certainty evidence) (Figure 7; Analysis 4.1). When evaluated for clinical response using a 50% improvement in CPSR score as a cut-off, a similar percentage of participants achieved clinical response at eight weeks. Specifically, 46.7% (7/15) of the biofeedback group achieved clinical response compared to 45.5% (6/14) of participants in the cognitive therapy group (RR 1.09, 95% CI 0.48 to 2.45; n = 29; P = 0 .84, low-certainty evidence) (Figure 8; Analysis 4.2). The effect was small and chance cannot be ruled out.

Figure 7. Forest plot of comparison: 4 Biofeedback versus Counseling, outcome: 4.1 Symptom Improvement (measured by CPSR).

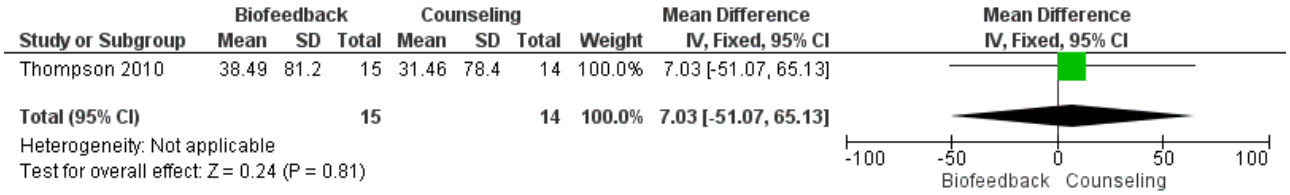
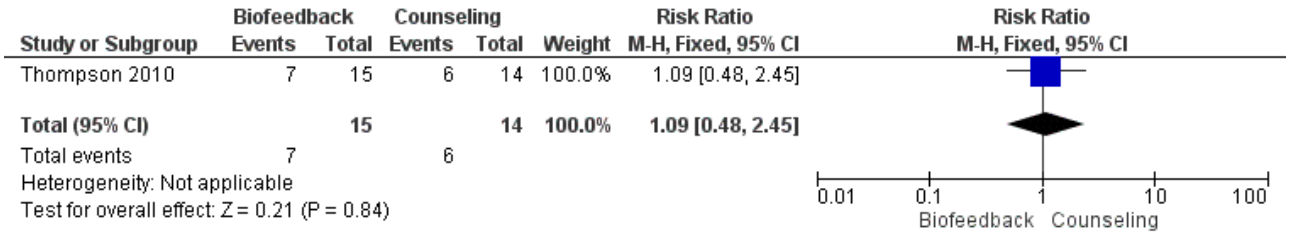


Figure 8. Forest plot of comparison: 4 Biofeedback versus Counseling, outcome: 4.2 Clinical Response (complete case).



Thompson 2010 also used the Cognitive Scale for Functional Bowel Disorders (CSFBD) as a measure of clinical improvement. This is a 25-item questionnaire that assesses the cognitions associated with functional bowel disorders on a scale of 1 to 7, generating a score between 25 and 175. Participants in the biofeedback and cognitive behavioral therapy group both improved on the CSFBD from baseline, but the trial authors did not note any between group differences, presented only statistical tests and did not provide summary effect sizes.

In a conference abstract report of a small RCT of 21 participants. Leahy 1997 compared electrocutaneous monitoring biofeedback to counseling, and measured "symptom scores" without further explanation. They reported that “counseling had no effect on symptom score”, with a change in median symptom score from 8.4 to 8.3 over the length of the study (Leahy 1997). The biofeedback arm was not reported as a complete arm, but rather as 'responders', with a median symptom score change of 7.7 to 5.6 over the length of the study, and 'non-responders', with a median score change from 7.8 to 8.5. Leahy 1997 did not adequately report the total endpoint scores between groups or statistical tests, making any effect of biofeedback difficult to interpret. The trial authors did not describe the type of counseling.

Multi-component psychological intervention (with biofeedback) versus no-treatment control

The CPSR score was a commonly used composite outcome measure for clinical improvement. With this measure, the larger the score, the larger the percentage reduction in IBS symptoms, with scores ranging from -100 to 100. Four trials used this measure, three of which examined the comparison of multi-component psychological intervention (with biofeedback) versus no-treatment control (Blanchard 1992a; Blanchard 1992b; Neff 1987). In the pooled analysis of these three trials, the mean difference favored the multi-component psychological intervention (with biofeedback) group compared to no-treatment control (MD 30.34, 95% CI 8.47 to 52.21; n = 101; P = 0.007; I^2 = 0%; very low-certainty evidence) (Figure 9; Analysis 5.1). These three studies also used an a priori determined 50% improvement in the CPSR score as a cut-off for 'clinical response'. In a pooled analysis, 55% (28/51) of the biofeedback group achieved clinical response compared to 26% (13/50) of the no-treatment control group (RR 2.12, 95% CI 1.24 to 3.62; NNTB = 4; n = 101, P = 0.006, I^2 = 0%, very low-certainty evidence) (Figure 10; Analysis 5.7).

Figure 9. Forest plot of comparison: 5 Multicomponent Psychological Intervention (with Biofeedback) versus no-treatment control, outcome: 5.1 Symptom Improvement (measured by CPSR).

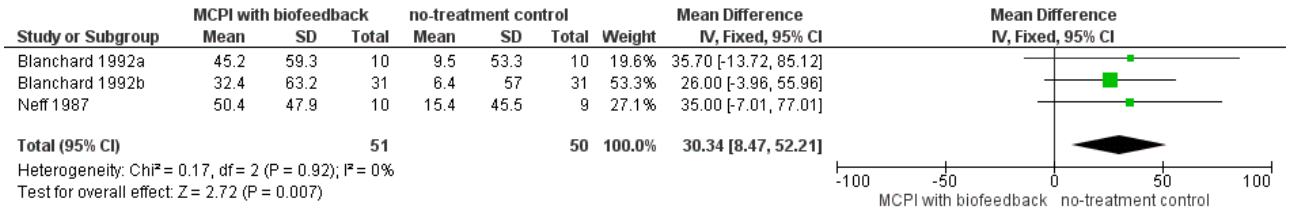
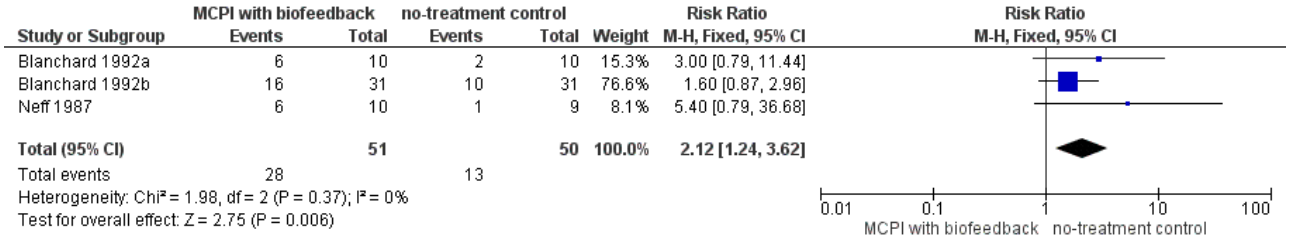


Figure 10. Forest plot of comparison: 5 Multicomponent Psychological Intervention (with Biofeedback) versus no-treatment control, outcome: 5.7 Clinical Response (complete case).



Multi-component psychological intervention (with biofeedback) versus attention control

Two studies compared a multi-component psychological intervention (with biofeedback) to an attention control (Blanchard 1992a; Blanchard 1992b). These studies used the CPSR score to measure clinical improvement. In the pooled analysis of these two studies, there was a marginal mean difference favoring the biofeedback group, but the effect of chance could not be ruled out (MD 4.02, 95% CI -21.41 to 29.45; n = 80; P = 0.76; I^2 = 0%; very low-certainty evidence) (Figure 11; Analysis 6.1). When evaluated for clinical response using a 50% improvement in CPSR score as an a priori cut-off, in pooled analysis (Figure 12; Analysis 6.2), a similar percentage of participants achieved clinical response at eight weeks. Specifically 54% (22/41) of the biofeedback group achieved clinical response compared to 49% (19/39) in the attention control group and the effect of chance could not be ruled out (RR 1.10, 95% CI 0.72 to 1.69; n = 80, P = 0.67, I^2 = 0%, very low-certainty evidence).

Figure 11. Forest plot of comparison: 6 Multicomponent Psychological Intervention (with Biofeedback) versus attention control, outcome: 6.1 Symptom Improvement (measured by CPSR).

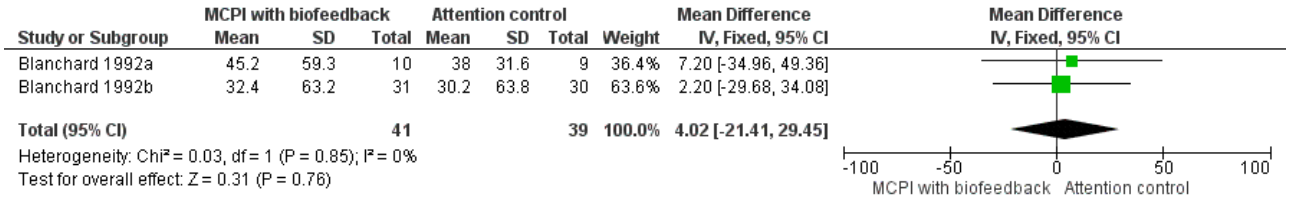
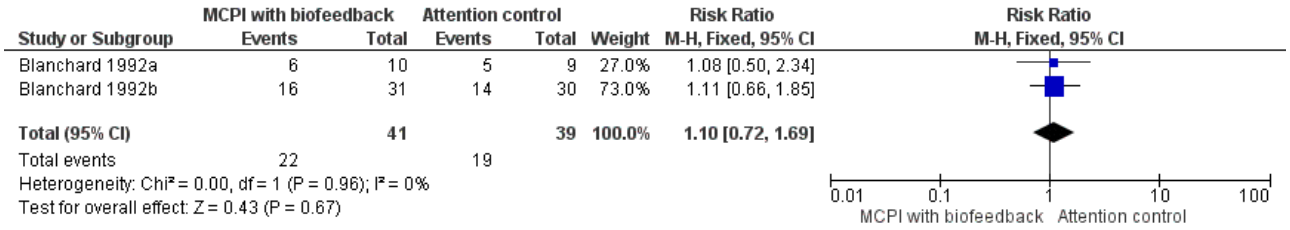


Figure 12. Forest plot of comparison: 6 Multicomponent Psychological Intervention (with Biofeedback) versus Attention control, outcome: 6.2 Clinical Response (complete case).



Biofeedback versus relaxation training

DeRoo 1988 compared rectosigmoidal biofeedback (n = 5) with a relaxation control (n = 5) and measured clinical improvement by severity of symptoms over eight weeks. The mean severity of symptoms in the biofeedback group was 3.20 at pretest and 2.80 post-test. The relaxation control group mean severity was 3.50 pretest and 2.50 post-test. The trial authors did not report standard deviations or between-group statistical tests.

Quality of life outcomes

Thompson 2010 used the Irritable Bowel Syndrome Impact Scale (IBS-IS), a 7-point quality of life scale that assesses impact of IBS on fatigue, daily activities, sleep, emotional health, and eating habits. None of the included trials used any other formal quality of life scales. Thompson 2010 compared heart rate variability biofeedback to a cognitive therapy active control in an eight week, two-armed trial (n = 29). The trial authors reported that both the biofeedback and cognitive therapy groups showed improvement in their IBS-IS score, but did not note any between-group differences or report any outcome data.

Secondary outcomes

Adverse events

While no adverse events were reported by any of the eight studies, only Thompson 2010 explicitly reported on adverse events (RD 0.00, 95% CI -0.12 to 0.12, n = 29, P = 1.00, low-certainty evidence) (Figure 13, Analysis 4.3; Figure 14; Analysis 4.4).

Figure 13. Forest plot of comparison: 4 Biofeedback versus Counseling, outcome: 4.3 Adverse Events.

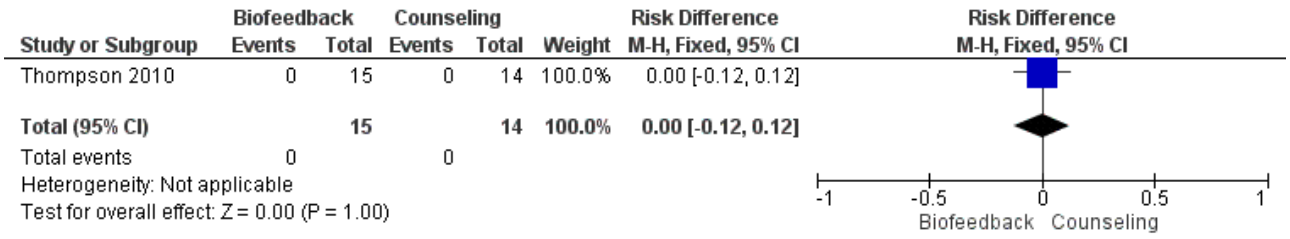
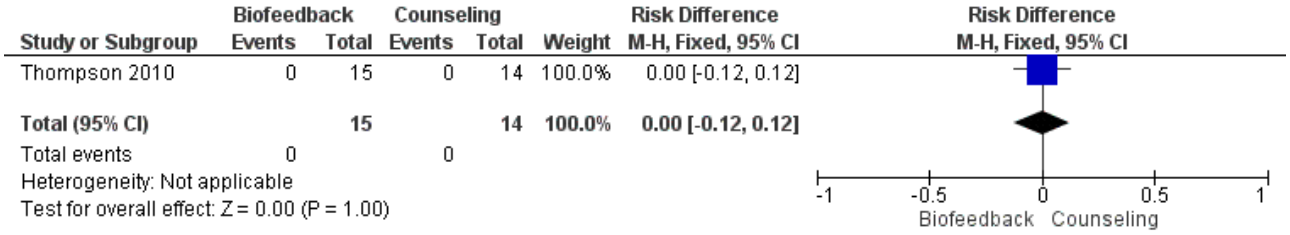


Figure 14. Forest plot of comparison: 4 Biofeedback versus Counseling, outcome: 4.4 Serious Adverse Events.



Withdrawal due to adverse events

None of the studies reported any withdrawals due to adverse events.

Serious adverse events

None of the studies reported any serious adverse events.

Stool frequency

None of the trials reported outcome-level data for stool frequency. However, DeRoo 1988 measured stool frequency using participant diaries, and reported a decrease in stool frequency in all three study arms (but did not report outcome-level data for between-group differences).

Stool consistency

Trembach 2009 used the Bristol Stool Scale (BSS) to report stool consistency. Mean BSS scores improved from 1.4 to 4 in the biofeedback group, and from 1.0 to 1.6 in the active controls. The trial authors did not report statistical tests of between-group differences.

IBS-constipation predominant stool frequency weekly responder (FDA definition)

None of the studies used this outcome.

IBS-diarrhea predominant stool frequency weekly responder (FDA definition)

None of the studies used this outcome.

Improvement in abdominal pain

Nine of the studies reported outcome-level data on abdominal pain (Blanchard 1992a; Blanchard 1992b, DeRoo 1988; Neff 1987; Thompson 2010, Trembach 2009). These studies reported on results from six comparisons as delineated below, grouped by comparison.

Biofeedback plus standard therapy versus standard therapy

Trembach 2009 had participants rate their abdominal pain using a scale of 0 to 3 (no pain to severe). Mean pain scores reduced from 2.2 to 0.0 after one month and 0.6 after six months in the biofeedback plus standard therapy group, compared with a drop from 2.2 to 0.6 after one month and 1.2 after six months in the standard therapy group. The trial authors did not provide SD or P values.

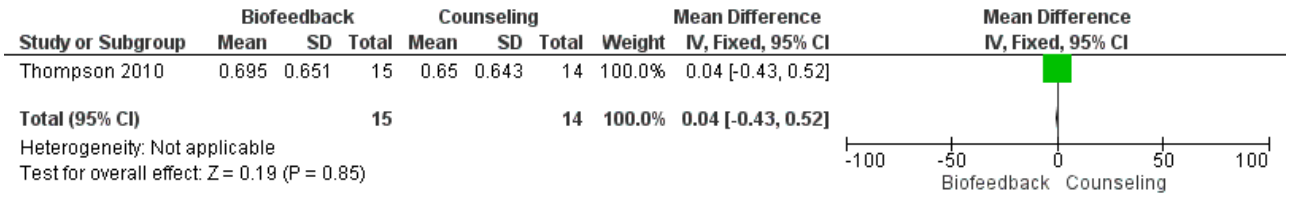
Biofeedback plus standard therapy versus sham biofeedback plus standard therapy

Trembach 2009 had participants rate their abdominal pain using a scale of 0 to 3 (no pain to severe). Mean pain scores reduced from 2.2 to 0.0 after one month and 0.6 after six months in the biofeedback plus standard therapy group compared with a drop from 2.1 to 0.6 after one month and 1.0 after six months in the standard therapy group. The trial authors did not provide SD or P values.

Biofeedback versus counseling

Thompson 2010 used a 0 to 4-point scale (no pain to severe pain) to track abdominal pain levels, and reported similar decreases in pain levels in both groups. The trial authors reported mean pain ratings post-treatment of 0.650 and 0.695 respectively for cognitive therapy and biofeedback (MD 0.04, 95% CI -0.43 to 0.52; n = 29; P = 0.85; low certainty evidence) (Figure 15; Analysis 4.5). The difference was small and chance cannot be ruled out.

Figure 15. Forest plot of comparison: 4 Biofeedback versus Counseling, outcome: 4.5 Abdominal Pain.

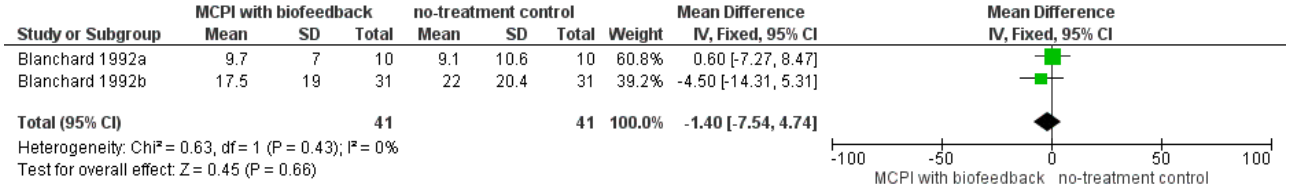


Multi-component psychological intervention (with biofeedback) versus no-treatment control

The three trials that compared multi-component psychological intervention including biofeedback versus no-treatment control all used symptom diaries to track abdominal pain, on a scale that was not fully described (Blanchard 1992a; Blanchard 1992b; Neff 1987). Neff 1987 did not provide enough information for pooling, but reported that mean abdominal pain scores improved during

the length of the study in both the biofeedback and no-treatment control group (6.82 to 2.54 and 9.36 to 8.80 respectively). The authors only reported that the effects of biofeedback were not statistically significant (they did not provide the P values and it is unclear if they are referring to a between-group or within-group comparison). Using pooled data from Blanchard 1992a and Blanchard 1992b, the pooled mean difference post-treatment using this abdominal pain scale favored the biofeedback arm (MD -1.40, 95% CI -7.54 to 4.74; n = 82; P = 0.66; very low-certainty evidence) (Figure 16; Analysis 5.11) but the effect was small and chance cannot be ruled out.

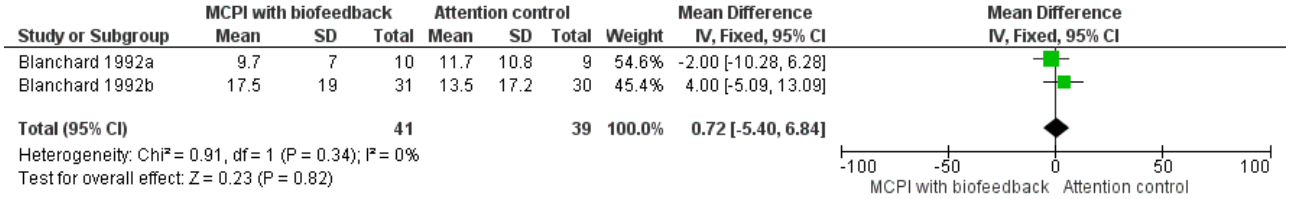
Figure 16. Forest plot of comparison: 5 Multicomponent Psychological Intervention (with Biofeedback) versus No-treatment control, outcome: 5.11 Abdominal Pain.



Multi-component psychological intervention (with biofeedback) versus attention control

The two trials that compared multi-component psychological intervention including biofeedback versus attention control used symptom diaries to track abdominal pain using a scale that was not fully described (Blanchard 1992a; Blanchard 1992b). The pooled mean difference post-treatment using this scale favored the attention control (MD 0.72, 95% CI -5.40 to 6.84; n = 80; P = 0.82; very low-certainty evidence) (Figure 17; Analysis 6.3) but the effect was small and chance cannot be ruled out (Blanchard 1992a; Blanchard 1992b).

Figure 17. Forest plot of comparison: 6 Multicomponent Psychological Intervention (with Biofeedback) versus Attention control, outcome: 6.3 Abdominal Pain.



Biofeedback versus relaxation training

DeRoo 1988 used a 0 to 4-point scale to measure abdominal pain (no pain to severe pain) and reported that there was no difference between groups in abdominal pain (the trial authors only reported statistical tests, not summary effect sizes).

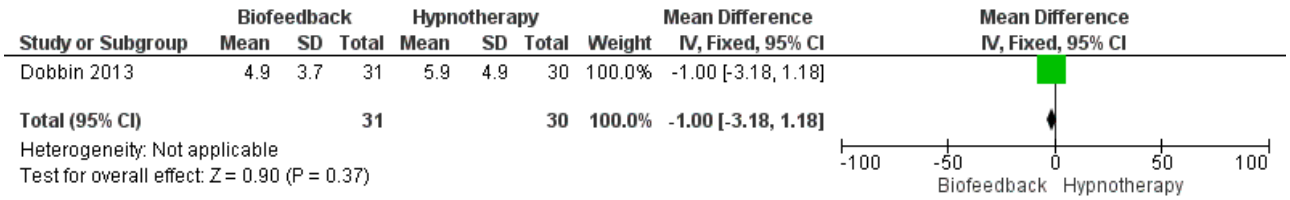
Depression

Outcome-level data on depression was reported in four of the eight included studies (Blanchard 1992a; Blanchard 1992b, DeRoo 1988; Dobbin 2013). These studies reported on results from four comparisons as delineated below, grouped by comparison.

Biofeedback versus hypnotherapy

Dobbin 2013 used the Hospital Anxiety and Depression Scale (HADS) to report the impact of the intervention on depression. They reported 12-week primary endpoint depression subscores of 4.9 for biofeedback and 5.9 for hypnotherapy. Although the MD favored biofeedback, the difference was small and the effect of chance cannot be ruled out (MD -1.00, 95% CI -3.18 to 1.18; n = 61; P = 0.37; low-certainty evidence) (Figure 18; Analysis 3.2)

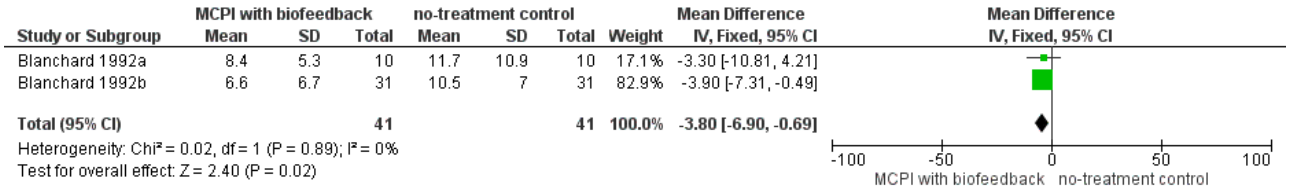
Figure 18. Forest plot of comparison: 3 Biofeedback versus Hypnotherapy, outcome: 3.2 Depression.



Multi-component psychological intervention (with biofeedback) versus no-treatment control

Blanchard 1992a and Blanchard 1992b both used the Beck Depression Inventory. In pooled analysis of these two trials, the MD favored the multi-component psychological intervention (with biofeedback) group compared to no-treatment control (MD -3.80, 95% CI -6.90 to -0.69; n = 82; P = 0.02, I^2 = 0%; very low-certainty evidence) (Figure 19; Analysis 5.12).

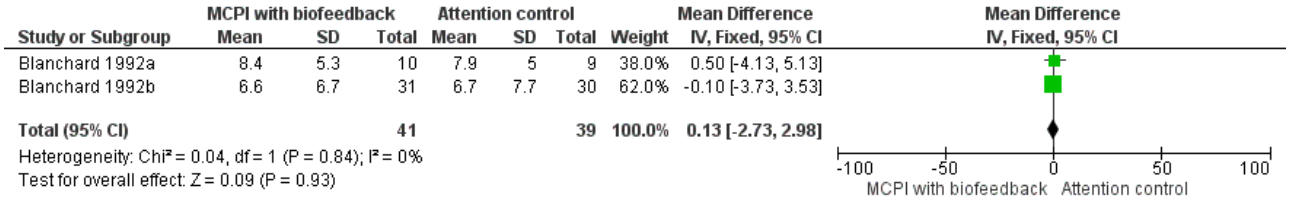
Figure 19. Forest plot of comparison: 5 Multicomponent Psychological Intervention (with Biofeedback) versus No-treatment control, outcome: 5.12 Depression.



Multi-component psychological intervention (with biofeedback) versus attention control

Blanchard 1992a and Blanchard 1992b both used the Beck Depression Inventory. In pooled analysis of these two trials, the MD favored the attention control group (MD 0.13, 95% CI -2.73 to 2.98; n = 80; P = 0.84, I^2 = 0%; very low-certainty evidence) (Figure 20; Analysis 6.4).

Figure 20. Forest plot of comparison: 6 Multicomponent Psychological Intervention (with Biofeedback) versus Attention control, outcome: 6.4 Depression.



Biofeedback versus relaxation training

DeRoo 1988 reported depression scores from a depression subcategory of the HCL 90-R. They reported that all groups had an improvement from baseline to post-treatment, but the between-group comparisons were similar (P = 0.60). The trial authors did not report group-level effect sizes or within-group P values.

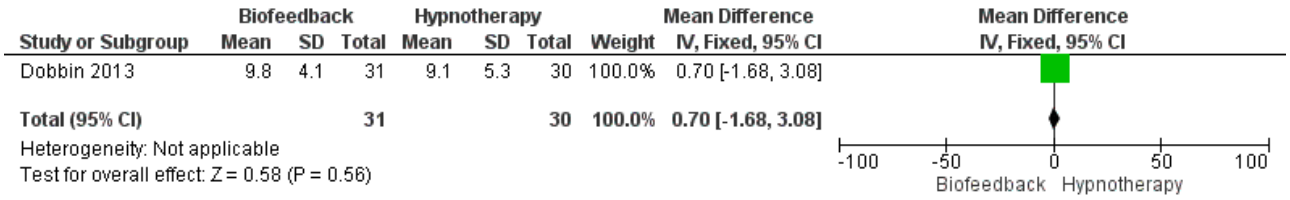
Anxiety

Outcome level data on anxiety was reported in four of the eight included studies (Blanchard 1992a; Blanchard 1992b, DeRoo 1988; Dobbin 2013). These studies reported on results from four comparisons as delineated below, grouped by comparison

Biofeedback versus hypnotherapy

Dobbin 2013 used the HADS to report the impact of the intervention on anxiety. They reported 12-week primary endpoint anxiety subscores of 9.8 for biofeedback and 9.1 for hypnotherapy (MD 0.70, 95% CI -1.68 to 3.08; n = 61; P = 0.56; low-certainty evidence) (Figure 21; Analysis 3.3).

Figure 21. Forest plot of comparison: 3 Biofeedback versus Hypnotherapy, outcome: 3.3 Anxiety.



Multi-component psychological intervention (with biofeedback) versus no-treatment control

Blanchard 1992a and Blanchard 1992b both used the State-Trait Anxiety Inventory. In a pooled analysis of these two trials, the MD for state anxiety favored the multi-component psychological intervention (with biofeedback) group compared to no-treatment control (MD -8.63, 95% CI -12.48 to -4.77; n = 82; P < 0.01, I^2 = 0%; very low-certainty evidence) (Figure 22; Analysis 5.13). The MD for trait anxiety favored the multi-component psychological intervention (with biofeedback) group compared to no-treatment control (MD -3.98, 95% CI -7.96 to -0.00; n = 82; P = 0.05, I^2 = 51%; very low-certainty evidence) (Figure 23; Analysis 5.14).

Figure 22. Forest plot of comparison: 5 Multicomponent Psychological Intervention (with Biofeedback) versus No-treatment control, outcome: 5.13 Anxiety - State.

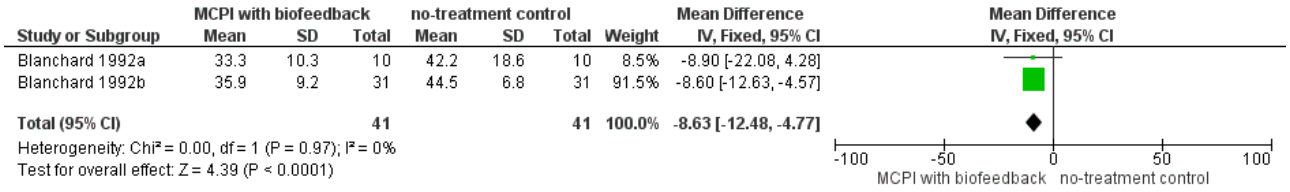
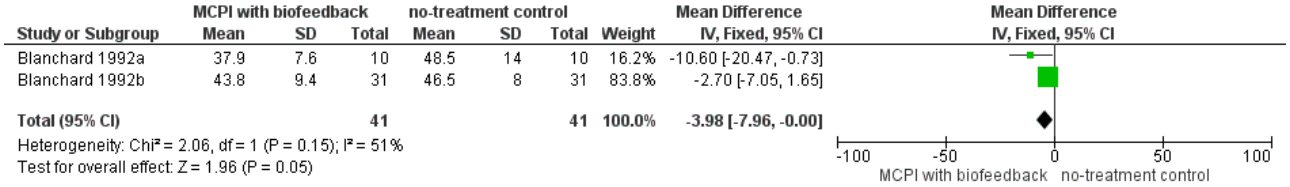


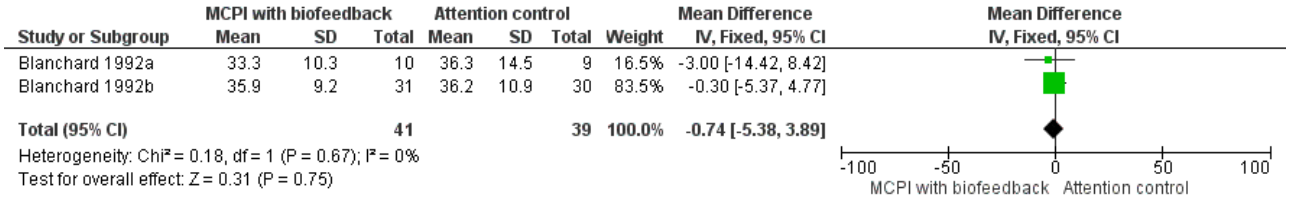
Figure 23. Forest plot of comparison: 5 Multicomponent Psychological Intervention (with Biofeedback) versus No-treatment control, outcome: 5.14 Anxiety - Trait.



Multi-component psychological intervention (with biofeedback) versus attention control

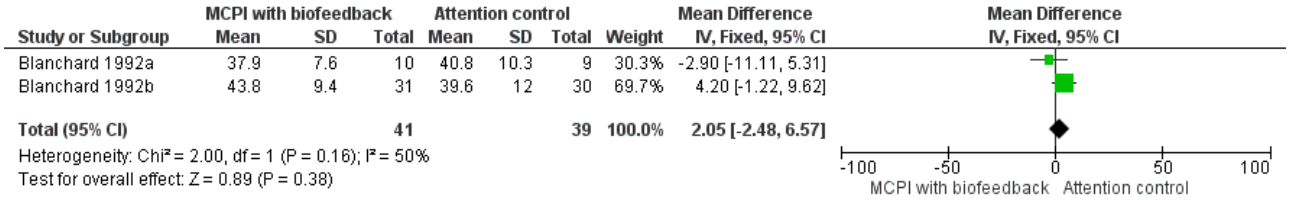
Blanchard 1992a and Blanchard 1992b both used the State-Trait Anxiety Inventory. In pooled analysis of these two trials, the MD for state anxiety favored the multi-component psychological intervention (with biofeedback) group compared to attention control, although the difference was small and the effects of chance cannot be ruled out (MD -0.74, 95% CI -5.38 to 3.89; n = 82; P = 0.75, I^2 = 0%; very low-certainty evidence) (Figure 24; Analysis 6.5).

Figure 24. Forest plot of comparison: 6 Multicomponent Psychological Intervention (with Biofeedback) versus Attention control, outcome: 6.5 Anxiety - State.



For trait anxiety, the MD favored the attention control, although the difference was small and the effects of chance cannot be ruled out (MD 2.05, 95% CI -2.05 to 6.57; n = 82; P = 0.38, I^2 = 50%; very low-certainty evidence) (Figure 25; Analysis 6.6).

Figure 25. Forest plot of comparison: 6 Multicomponent Psychological Intervention (with Biofeedback) versus Attention control, outcome: 6.6 Anxiety - Trait.



Biofeedback versus relaxation training

DeRoo 1988 reported anxiety scores from an anxiety subcategory of the HCL 90-R. They reported that all groups had improvement pre/post-treatment (P < 0.007) but that the between group comparisons were equivalent. The trial authors did not provide group-level effect sizes or specific between- and within-group P values).

Sensitivity Analyses

We conducted sensitivity analyses in order to determine the role that meta-analysis model (random versus fixed) and missing outcome data played on our primary outcome results. Because of the identical nature of the intervention, control, and outcome measure, we chose to meta-analyze the following comparisons

using a fixed-effect model as a primary analysis: multi-component psychological intervention (with biofeedback) versus no-treatment control and multi-component psychological intervention (with biofeedback) versus attention control. We then conducted sensitivity analysis using a random-effects model (Analysis 5.2 for symptom improvement; Analysis 5.8 for clinical response). When using a random-effects model, the effect size was marginally smaller, but still favored biofeedback and the effect estimate survived the sensitivity analysis (Analysis 5.8).

As there were some missing outcome data in two of the three meta-analyzed trials for our primary outcome of clinical improvement (Blanchard 1992b; Neff 1987), we also conducted a sensitivity analysis using GRADE guidance for handling missing outcome data (Guyatt 2017). For the dichotomous outcome of clinical responder in the comparison of multi-component psychological intervention (with biofeedback) versus no-treatment control, the effect decreased as we increased the strictness of the assumptions. At a 2:1 ratio, we assumed that all participants with missing outcome data in the biofeedback group had been non-responders. This assumption led to a lower effect estimate, but still favored biofeedback and the effect estimate survived the sensitivity analysis (Analysis 5.10).

We carried out the missing data sensitivity analysis for the continuous outcome 'symptom improvement', in the comparison of multi-component psychological intervention (with biofeedback) versus no-treatment control. In this analysis, the effect decreased as increasing levels of sensitivity assumptions were made. However, even with the strictest assumptions, the effect estimate still favored biofeedback and the effect estimate survived the sensitivity analysis (Analysis 5.6).

demonstrated that the benefit was not robust to all assumptions. With the strictest assumption, the effect decreased and the effects of chance could not be ruled out (Analysis 3.7).

DISCUSSION

Summary of main results

We identified eight small randomized trials (n = 300) of biofeedback that met our inclusion criteria. Overall, low to very low-certainty evidence demonstrated no benefit to a moderate clinically important benefit of biofeedback versus non-active and active (e.g. hypnotherapy) controls. One study suggested a moderate clinically important benefit of electrocutaneous resistance biofeedback when used in combination with standard IBS treatment, when compared to both standard therapy alone and standard therapy with sham biofeedback (Trembach 2009). We noted a small, but clinically important, benefit with heart rate variability biofeedback when compared to hypnotherapy (Dobbin 2013). We observed a small benefit for biofeedback compared to counseling, but could not rule out the effect of chance (Thompson 2010; Leahy 1997). We noted a moderate clinically important benefit for a multi-component psychological intervention, which included thermal biofeedback, compared to no-treatment control (Blanchard 1992a). However, we could not rule out the effect of chance when this intervention was compared to an attention control (Blanchard 1992b). Rectosigmoidal biofeedback showed less clinical benefit than relaxation control, but we could not rule out the effect of chance (DeRoo 1988).

Of the eight included studies, only one formally measured quality of life (Thompson 2010). In comparing heart rate variability biofeedback to a cognitive therapy active control, both the biofeedback and cognitive therapy groups showed improvement in their IBS-IS score but the trial authors did not note any between-group differences or report any outcome data.

Overall completeness and applicability of evidence

Participants were more likely to be female, and clustered in age near 40 (though many trials only reported mean age). The recruiting for these trials also suggests that they were largely limited to people who already had access to medical care. As such, the applicability of these results to children, the elderly, and underserved populations is uncertain.

The AAPB defines biofeedback as “a process that enables an individual to learn how to change physiological activity for the purposes of improving health and performance”(AAPB 2016). Germane to this definition is that the use of an appropriate biofeedback intervention involves a change in physiological activity (e.g. change in heart rate variability, skin temperature, etc.), and that such change may improve health outcomes. In the studies included in our systematic review, the majority of researchers did not report baseline physiological measurements consistent with autonomic nervous system (ANS) functioning, nor did they report physiological response or non-response to biofeedback treatment. According to the autonomic nervous system hypothesis of IBS, individuals with IBS are more prone towards increased sympathetic and decreased parasympathetic nervous system activity (Manabe 2009). Since these studies did not report baseline measures of physiological activity indicative of autonomic nervous system function, it is unclear whether or not the individuals included in these studies would have been considered ANS-normal or ANS-abnormal at the start of the treatment intervention. In addition, while these studies reported on clinical response by the end of the intervention period, they did not clearly report physiological response. Finally, the durability of physiological change (e.g. sustainability of change over time), which is an important part of clinical biofeedback, was not reported in these studies. These concerns collectively speak to the applicability of this evidence to real world biofeedback, in which physiological baseline and response to therapy is an important component of treatment (Schartz 2003). While reporting on results of an IBS cohort regardless of physiologic status limits selection bias, additional reporting on physiologic responders as a subgroup may more appropriately mimic real world practice.

Quality of the evidence

There are large non-specific effects of intervention (i.e. placebo effects) in IBS studies in general, especially when the intervention arm is complex and the provider-patient interaction is substantial, such as with biofeedback (Kaptchuk 2008). Additionally, blinding of intervention is difficult with biofeedback, and IBS outcome measures are subjectively reported. There is meta-epidemiologic evidence to suggest large biases in unmasked trials when subjective outcome measures are used (Wood 2008).

For these and other reasons, as discussed in the Characteristics of included studies tables below, we believe that all eight of our included studies were high or unclear in their risk of bias.

We used GRADE criteria to assess the overall certainty of evidence for all comparisons for the primary outcomes, as well as the secondary outcomes of adverse events, serious adverse events, pain, depression, and anxiety, when possible. All GRADE assessments are reported in the 'Summary of findings' tables. GRADE evaluations ranged from very low to low, indicating that we have very little certainty in the effect estimates for some outcomes, and for others our certainty is very limited.

For the primary outcome of clinical/global improvement, we gave a low-certainty rating to the comparison of a multi-component psychological intervention (with biofeedback) versus no-treatment control. The estimated effect was an improvement of 30 points on the CPSR scale and a risk ratio of 2.12 for clinical response, favoring biofeedback. When we compared the same biofeedback intervention to an attention control, we found the estimated effect of a 4-point improvement on the CPSR scale and a risk ratio of 1.10 for clinical response to be very low certainty as well. We had low certainty in the estimated improvement of 59 points on the IBS-SSS scale when we compared biofeedback to hypnotherapy and low certainty in the 7-point CPSR improvement when we compared biofeedback to counseling. We had very low certainty in the small estimated mean difference of 0.30 in symptom severity, favoring the relaxation control, when we compared rectosigmoidal biofeedback to a relaxation control. Finally, we had very low certainty in the estimated risk ratio of 4.20, favoring biofeedback, for clinical response when we compared 'biofeedback with standard therapy' to standard therapy alone. We also had low certainty in the risk ratio of 2.33 when we compared 'biofeedback with standard therapy' with 'sham biofeedback and standard therapy'.

Potential biases in the review process

While we attempted to locate each of the articles identified in our literature review, there were nine studies that, despite considerable effort, we were unable to locate for the review and could not assess for potential inclusion. It is possible that one or more of these studies could have led to a change in our conclusion.

Our approach to assessment of performance bias is arguably potentially overly conservative for active control comparisons and potentially under conservative for attention control comparisons. However, this decision was based on published literature on non-specific effects in IBS using elaborate 'interventions' (Kaptchuk 2008), which we argue is appropriate in an elaborate modality such as biofeedback, We were consistent in this approach across the studies we evaluated. Additionally, pragmatically because it meant we would err on assessing performance bias as unclear when others might consider it low for active control comparisons, this would lead to a more conservative estimation in our a priori sensitivity analyses based on low versus high/unclear risk of bias studies. Conversely, for attention control comparisons, the determination between high or unclear would not impact on sensitivity analysis as high and unclear studies would be grouped together anyway. While other people may disagree, our approach was applied consistently across studies, was based on published literature, and pragmatically led to a more conservative methodology.

We followed consensus guidelines and did not conduct a formal publication bias assessment because we had less than 10 trials per outcome (Sterne 2011).

Agreements and disagreements with other studies or reviews

We are unaware of other systematic reviews of this subject.

AUTHORS' CONCLUSIONS

Implications for practice

There is not currently enough evidence to assess whether biofeedback interventions are effective for controlling symptoms of irritable bowel syndrome (IBS). Some positive results have been reported in small studies. While the effect estimates suggests a benefit of biofeedback when used as part of a multi-component psychological intervention, compared to a no-treatment control, for clinical symptoms, depression, and anxiety, in the context of the very low quality of evidence we cannot be certain if there is an effect or not. Compared to hypnotherapy, biofeedback may reduce IBS symptoms. When compared to counseling, biofeedback appears not to reduce overall IBS symptoms or abdominal pain. When biofeedback is used with standard therapy and compared to standard therapy alone or with sham biofeedback, biofeedback may lead to overall symptom reduction.

Implications for research

Upon review of the available randomized clinical trial evidence on biofeedback for IBS, we noted several areas of deficit that would benefit from targeted future research, as delineated below.

1. Utilization of active control groups that use high provider-patient interaction, in an attempt to balance non-specific effects of intervention between groups.
2. Implementation of commonly used outcome measures (e.g. IBS-symptom severity score [IBS-SSS]) that are most important to people with IBS, as well as historical outcome measures (e.g. composite primary symptom reduction score [CPSR]) to allow for meta-analysis with previous studies.
3. Larger trials enrolling 100 or more participants.
4. Future trials should focus on biofeedback forms showing preliminary benefit, as identified as in this review (e.g. heart rate variability).
5. No identified trials compared different modalities of biofeedback in head to head comparisons; such trial design would help inform if efficacy should be best viewed as a class effect or if specific biofeedback types (e.g. heart rate variability versus skin conductance) show superiority or non-inferiority.
6. Whilst we do value multi-component intervention research, such designs make attribution of effect to biofeedback, specifically, impossible. Future research in this early phase of the evidence base should focus on efficacy of the individual biofeedback interventions.
7. Future studies should measure baseline autonomic nervous system function with validated measures and methodologies, with the goal of classifying participants as autonomic nervous system (ANS)-normal or ANS-abnormal.
8. Future studies should measure post-treatment ANS function and compare these measurements with baseline ANS measures, with the aim of classifying participants as physiological responders and non-responders to biofeedback treatment.

9. Future studies should aim to determine the durability of physiological change over-time and to correlate this change with any improvements (transient or stable) in IBS symptoms.
10. Studies should closely examine the correlation between IBS symptom improvement and physiological response and non-response to biofeedback treatment with the aim of further clarifying placebo effects versus true effects of treatment.
11. Future studies should closely examine medication status of the participants with respect to medications which may alter ANS function, thus potentially confounding the effects of biofeedback treatment.

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* Indicates the major publication for the study

CHARACTERISTICS OF STUDIES

Characteristics of included studies *[ordered by study ID]*

Blanchard 1992a

Methods	3 arm RCT
Participants	n = 30 adult participants with IBS (unclear what percentage had which IBS subtype); 10 participants in each treatment group; age range 23-76; USA
Interventions	(1) multi-component psychological treatment which included thermal biofeedback (2) 'pseudomeditation' attention control

Blanchard 1992a *(Continued)*

	(3) symptom monitoring
Outcomes	Assessments at baseline and after 8 weeks of treatment with a global assessment scale. Secondary outcome measures included assessment of abdominal pain, depression, and anxiety.
Notes	Unclear funding source. Please note that this study and Blanchard 1992b are separate studies reported in the same publication.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Not described
Allocation concealment (selection bias)	Unclear risk	Not described
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	There appears to be blinding between the active and attention control groups for participants, but not for the personnel or for the wait-list control.
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Outcome assessors were the participants. Active group and attention control were likely to have been adequately blinded, and any comparison between these groups would be low risk. However, any comparison with the wait-list control would not be.
Incomplete outcome data (attrition bias) All outcomes	Low risk	No missing outcome data
Selective reporting (reporting bias)	Low risk	Outcomes reported match methods
Other bias	Low risk	None noted

Blanchard 1992b

Methods	3 arm RCT comparing 8 weeks of skin conductance biofeedback with stress reduction techniques to an attention control and no-treatment control.
Participants	n = 92 adult participant with IBS (28 IBS-D, 23 IBS-C, 41 IBS-M), average age = 43.4, USA
Interventions	(1) multi-component psychological treatment, which included thermal biofeedback (n = 31) (2) 'pseudomeditation' attention control (n = 30) (3) symptom monitoring (n = 31)
Outcomes	Assessments at baseline and after 8 weeks of treatment with a global symptom assessment scale. Secondary outcome measures included assessment of abdominal pain, depression, and anxiety.
Notes	Unclear funding source

Blanchard 1992b *(Continued)*

Please note that this study and Blanchard 1992a are separate studies reported in the same publication.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Not described
Allocation concealment (selection bias)	Unclear risk	Not described
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Not clear if there was blinding regarding which of the active groups was the group of interest.
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Not clear if there was blinding regarding which of the active groups was the group of interest.
Incomplete outcome data (attrition bias) All outcomes	High risk	> 10% missing data
Selective reporting (reporting bias)	Low risk	outcomes reported match methods
Other bias	Low risk	None noted

DeRoo 1988

Methods	3 arm RCT compared biofeedback (n = 5) with a relaxation control (n = 5) and a sham biofeedback control (n = 3). While the text is unclear, it appears only the biofeedback arm and the relaxation arm were truly randomized and so the third arm was not included in analysis.
Participants	13 adult men and women in US with IBS-D, average age of 41.7
Interventions	Biofeedback used rectosigmoidal manometry as teaching tool for 5 to 8 1-hour sessions.
Outcomes	Assessment by scale at baseline and after 5 to 8 sessions. Secondary outcome measures assessed stool frequency, abdominal pain, anxiety, and depression
Notes	Not clearly reported how many participants finished the trial and were assessed. This was a dissertation. Unclear funding source.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	No details on method
Allocation concealment (selection bias)	Unclear risk	Not discussed

DeRoo 1988 *(Continued)*

Blinding of participants and personnel (performance bias) All outcomes	High risk	Not discussed, likely unblinded
Blinding of outcome assessment (detection bias) All outcomes	High risk	Not discussed, likely unblinded
Incomplete outcome data (attrition bias) All outcomes	Low risk	No attrition
Selective reporting (reporting bias)	Low risk	All outcomes stated in methods are reported
Other bias	Low risk	None noted

Dobbin 2013

Methods	A 12-week unblinded RCT comparing biofeedback (n=31) and hypnotherapy (n=30) in the management of IBS.
Participants	61 women, age 18-60 with a diagnosis of IBS. Trial was in Scotland.
Interventions	Biofeedback measured heart rate variability during three 1-hour sessions. Participants also used techniques learned during sessions daily at home.
Outcomes	IBS-SSS and HADS at baseline and at 12 weeks
Notes	There was no untreated control condition. Unclear funding source

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	Block randomization
Allocation concealment (selection bias)	Unclear risk	Not described
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Since both groups got active intervention, should not be materially biased
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	See above, outcomes were measured by participant
Incomplete outcome data (attrition bias)	High risk	Dropouts exceeded 10%

Dobbin 2013 *(Continued)*

All outcomes		
Selective reporting (reporting bias)	Low risk	All outcomes assessed are reported
Other bias	Low risk	None noted

Leahy 1997

Methods	RCT comparing 4 sessions of biofeedback to counseling in management of IBS symptoms
Participants	21 adult UK residents with IBS (unclear what percentage had which IBS subtype, or how many participants were in each treatment group).
Interventions	Electrocutaneous monitoring with video feedback
Outcomes	Participants were assessed using a scale developed by the authors at baseline and after the intervention
Notes	Trial reported as abstract only. Unclear funding source

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	Randomization not described
Allocation concealment (selection bias)	Unclear risk	Not reported
Blinding of participants and personnel (performance bias) All outcomes	High risk	Not blinded. Each participant went through biofeedback in pilot, so would have known if in active treatment group
Blinding of outcome assessment (detection bias) All outcomes	High risk	Outcome assessors were also participants
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Only reported as abstract
Selective reporting (reporting bias)	Unclear risk	Only reported as abstract
Other bias	Unclear risk	Only reported as abstract

Neff 1987

Methods	RCT compared biofeedback (n = 10) with untreated controls (n = 9) in the management of IBS
Participants	19 US adults with IBS (7 IBS-D, 8 IBS-C, 4 IBS-M), average age 41 years, 6 male/14 female
Interventions	12 treatments of thermal biofeedback during relaxation training
Outcomes	Assessment of IBS symptoms and abdominal pain via self-developed scale at baseline and 2 weeks post-treatment
Notes	Assessments were over a daily average of the 2 weeks post-assessment, not a single day's symptoms. Unclear funding source

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Randomization procedure not described
Allocation concealment (selection bias)	Unclear risk	Not discussed
Blinding of participants and personnel (performance bias) All outcomes	High risk	Unblinded, controls were untreated
Blinding of outcome assessment (detection bias) All outcomes	High risk	Unblinded, controls were untreated
Incomplete outcome data (attrition bias) All outcomes	Low risk	Only 1 dropout
Selective reporting (reporting bias)	Unclear risk	It appears the outcomes chosen for the included trial (study 2 in the published report) were different from the outcome used in study 1, which was the pilot study for pilot 2. It is unclear why this change was made.
Other bias	Low risk	None noted

Thompson 2010

Methods	RCT comparing biofeedback (n = 19) and cognitive behavioral therapy (n = 18) for symptom management in IBS over an 8-week period.
Participants	37 adults with IBS (11 IBS-D, 15 IBS-C, 11 IBS-M), average age 54, 32 female/5 male; USA
Interventions	11 weekly treatments with biofeedback via heart rate variability and skin temperature
Outcomes	CFSBD was the key IBS specific outcome measure. A CPSR score was also calculated. Secondary outcome measures included IBS Impact Score and abdominal pain reporting.
Notes	Reporting on outcomes was unclear regarding the intervals of measurement. This was a dissertation.

Thompson 2010 *(Continued)*

	Unclear funding source

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Random number generator
Allocation concealment (selection bias)	Unclear risk	Not described
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Appears to have been unblinded, but controls were active treatment group
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Appears to have been unblinded, but controls were active treatment group
Incomplete outcome data (attrition bias) All outcomes	High risk	21% dropout rate. Dropouts were similar in active treatment groups, but reasons were not provided.
Selective reporting (reporting bias)	Low risk	Reported outcomes match methods
Other bias	Low risk	None noted

Trembach 2009

Methods	3 arm RCT comparing 'standard therapy' (fiber and medication) (n =10) to standard therapy plus biofeedback (n = 10) and what appears to be a sham biofeedback arm plus standard therapy (n =10).
Participants	30 Russian women aged 18-35 with non-diarrhea IBS
Interventions	Up to 6 months of biofeedback treatment using electrocutaneous resistance sensors
Outcomes	Constipation, abdominal pain, stool consistency (using the Brisol Stool Scale), and clinical improvement. Assessed at baseline, 1 month, and 6 months.
Notes	Frequency and duration of biofeedback treatments are unclear. The paper was translated from Russian. Unclear funding source

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Procedure not described

Trembach 2009 *(Continued)*

Allocation concealment (selection bias)	Unclear risk	Procedure not described
Blinding of participants and personnel (performance bias) All outcomes	High risk	Unblinded trial
Blinding of outcome assessment (detection bias) All outcomes	High risk	Unblinded trial
Incomplete outcome data (attrition bias) All outcomes	Low risk	No dropouts
Selective reporting (reporting bias)	Unclear risk	Protocol not available
Other bias	Low risk	None noted

RCT = randomized controlled trial; IBS = irritable bowel syndrome; IBS-C = IBS-constipation predominant; IBS-D = IBS-diarrhea predominant; IBS-M = IBS-mixed; IBS-SSS = IBS symptom severity score; HADS = hospital anxiety and depression scale; CFSBD = cognitive scale for functional bowel disorders; CPSR = composite primary symptom reduction score.

Characteristics of excluded studies *[ordered by study ID]*

Study	Reason for exclusion
Ahadi 2014	Not an RCT
Bergeron 1983	Not truly randomized
Bleijenberg 1994	Not IBS
Boyce 2003	Not biofeedback
Folgar 1995	Unable to acquire
Fu 2014	Unable to acquire
Grey 1983	Wrong study type - not randomized
Ryan 2004	Not exclusively IBS patients. Mixed groups of multiple functional bowel disorders. Results not differentiated by disorder type.
Singles 1989	Wrong population, not IBS
van der Plas 1994	Wrong population, not IBS

RCT = randomized controlled trial; IBS = irritable bowel syndrome

DATA AND ANALYSES

Comparison 1. Biofeedback plus standard therapy versus standard therapy

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Clinical Response	1	20	Risk Ratio (M-H, Fixed, 95% CI)	4.2 [1.40, 12.58]
2 Abdominal Pain (4 weeks)	1	20	Mean Difference (IV, Fixed, 95% CI)	0.0 [0.0, 0.0]
3 Abdominal Pain (6 months)	1	20	Mean Difference (IV, Fixed, 95% CI)	0.0 [0.0, 0.0]

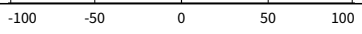
Analysis 1.1. Comparison 1 Biofeedback plus standard therapy versus standard therapy, Outcome 1 Clinical Response.

Study or subgroup	Biofeedback + standard therapy n/N	Standard therapy n/N	Risk Ratio M-H, Fixed, 95% CI	Weight	Risk Ratio M-H, Fixed, 95% CI
Trembach 2009	10/10	2/10		100%	4.2[1.4,12.58]
Total (95% CI)	**10**	**10**		**100%**	**4.2[1.4,12.58]**
Total events: 10 (Biofeedback + standard therapy), 2 (Standard therapy)					
Heterogeneity: Not applicable					
Test for overall effect: Z=2.56(P=0.01)					

Biofeedback + standard therapy — Standard therapy

Analysis 1.2. Comparison 1 Biofeedback plus standard therapy versus standard therapy, Outcome 2 Abdominal Pain (4 weeks).

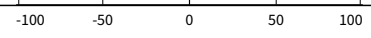
Study or subgroup	Biofeedback + standard therapy N	Biofeedback + standard therapy Mean(SD)	Standard therapy N	Standard therapy Mean(SD)	Mean Difference Fixed, 95% CI	Weight	Mean Difference Fixed, 95% CI
Trembach 2009	10	0 (0)	10	0.6 (0)			Not estimable
Total ***	**10**		**10**				**Not estimable**
Heterogeneity: Not applicable							
Test for overall effect: Not applicable							



Biofeedback + standard therapy — Standard therapy

Analysis 1.3. Comparison 1 Biofeedback plus standard therapy versus standard therapy, Outcome 3 Abdominal Pain (6 months).

Study or subgroup	Biofeedback + standard therapy N	Mean(SD)	Standard therapy N	Mean(SD)	Mean Difference Fixed, 95% CI	Weight	Mean Difference Fixed, 95% CI
Trembach 2009	10	0.6 (0)	10	1.2 (0)			Not estimable
Total ***	**10**		**10**				**Not estimable**
Heterogeneity: Not applicable							
Test for overall effect: Not applicable							



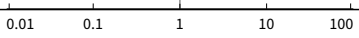
Biofeedback + standard therapy — Standard therapy

Comparison 2. Biofeedback plus standard therapy versus sham biofeedback plus standard therapy

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Clinical Response	1	20	Risk Ratio (M-H, Fixed, 95% CI)	2.33 [1.13, 4.80]
2 Abdominal Pain (4 weeks)	1	20	Mean Difference (IV, Fixed, 95% CI)	0.0 [0.0, 0.0]
3 Abdominal Pain (6 months)	1	20	Mean Difference (IV, Fixed, 95% CI)	0.0 [0.0, 0.0]

Analysis 2.1. Comparison 2 Biofeedback plus standard therapy versus sham biofeedback plus standard therapy, Outcome 1 Clinical Response.

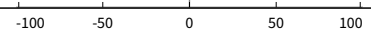
Study or subgroup	Biofeedback + standard therapy n/N	Sham biofeedback + standard therapy n/N	Risk Ratio M-H, Fixed, 95% CI	Weight	Risk Ratio M-H, Fixed, 95% CI
Trembach 2009	10/10	4/10		100%	2.33[1.13,4.8]
Total (95% CI)	**10**	**10**		**100%**	**2.33[1.13,4.8]**
Total events: 10 (Biofeedback + standard therapy), 4 (Sham biofeedback + standard therapy)					
Heterogeneity: Not applicable					
Test for overall effect: Z=2.3(P=0.02)					



Biofeedback + standard therapy — Sham biofeedback + standard therapy

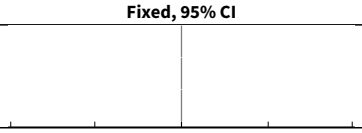
Analysis 2.2. Comparison 2 Biofeedback plus standard therapy versus sham biofeedback plus standard therapy, Outcome 2 Abdominal Pain (4 weeks).

Study or subgroup	Biofeedback + standard therapy N	Mean(SD)	Sham biofeedback + standard therapy N	Mean(SD)	Mean Difference Fixed, 95% CI	Weight	Mean Difference Fixed, 95% CI
Trembach 2009	10	0 (0)	10	0.6 (0)			Not estimable



Biofeedback + standard therapy — Sham biofeedback + standard therapy

Study or subgroup	Biofeedback + standard therapy		Sham biofeedback + standard therapy		Mean Difference	Weight	Mean Difference
	N	Mean(SD)	N	Mean(SD)	Fixed, 95% CI		Fixed, 95% CI
Total ***	**10**		**10**				**Not estimable**
Heterogeneity: Not applicable							
Test for overall effect: Not applicable							



Analysis 2.3. Comparison 2 Biofeedback plus standard therapy versus sham biofeedback plus standard therapy, Outcome 3 Abdominal Pain (6 months).

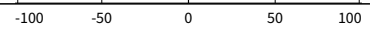
Study or subgroup	Biofeedback + standard therapy		Sham biofeedback + standard therapy		Mean Difference	Weight	Mean Difference
	N	Mean(SD)	N	Mean(SD)	Fixed, 95% CI		Fixed, 95% CI
Trembach 2009	10	0 (0)	10	1 (0)			Not estimable
Total ***	**10**		**10**				**Not estimable**
Heterogeneity: Not applicable							
Test for overall effect: Not applicable							

Comparison 3. Biofeedback versus hypnotherapy

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Symptom Improvement (measured by IBS-SSS)	1	61	Mean Difference (IV, Fixed, 95% CI)	-58.8 [-109.11, -8.49]
2 Depression	1	61	Mean Difference (IV, Fixed, 95% CI)	-1.0 [-3.18, 1.18]
3 Anxiety	1	61	Mean Difference (IV, Fixed, 95% CI)	0.70 [-1.68, 3.08]
4 Symptom Improvement (measured by IBS-SSS) - Sensitivity Analysis Strategy 1	1	76	Mean Difference (IV, Fixed, 95% CI)	-47.97 [-93.09, -2.85]
5 Symptom Improvement (measured by IBS-SSS) - Sensitivity Analysis Strategy 2	1	76	Mean Difference (IV, Fixed, 95% CI)	-58.8 [-103.92, -13.68]
6 Symptom Improvement (measured by IBS-SSS) - Sensitivity Analysis Strategy 3	1	76	Mean Difference (IV, Fixed, 95% CI)	-47.97 [-93.09, -2.85]
7 Symptom Improvement (measured by IBS-SSS) - Sensitivity Analysis Strategy 4	1	76	Mean Difference (IV, Fixed, 95% CI)	-35.59 [-80.71, 9.53]

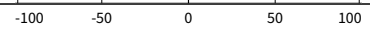
Analysis 3.1. Comparison 3 Biofeedback versus hypnotherapy, Outcome 1 Symptom Improvement (measured by IBS-SSS).

Study or subgroup	Biofeedback N	Biofeedback Mean(SD)	Hypnotherapy N	Hypnotherapy Mean(SD)	Mean Difference Fixed, 95% CI	Weight	Mean Difference Fixed, 95% CI
Dobbin 2013	31	-116.8 (99.3)	30	-58 (101.1)		100%	-58.8[-109.11,-8.49]
Total ***	**31**		**30**			**100%**	**-58.8[-109.11,-8.49]**
Heterogeneity: Not applicable							
Test for overall effect: Z=2.29(P=0.02)							



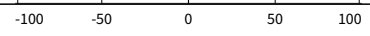
Analysis 3.2. Comparison 3 Biofeedback versus hypnotherapy, Outcome 2 Depression.

Study or subgroup	Biofeedback N	Biofeedback Mean(SD)	Hypnotherapy N	Hypnotherapy Mean(SD)	Mean Difference Fixed, 95% CI	Weight	Mean Difference Fixed, 95% CI
Dobbin 2013	31	4.9 (3.7)	30	5.9 (4.9)		100%	-1[-3.18,1.18]
Total ***	**31**		**30**			**100%**	**-1[-3.18,1.18]**
Heterogeneity: Not applicable							
Test for overall effect: Z=0.9(P=0.37)							



Analysis 3.3. Comparison 3 Biofeedback versus hypnotherapy, Outcome 3 Anxiety.

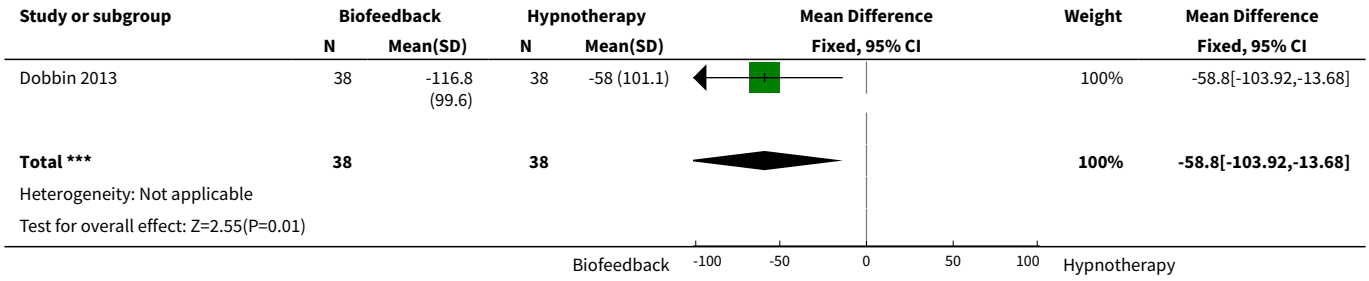
Study or subgroup	Biofeedback N	Biofeedback Mean(SD)	Hypnotherapy N	Hypnotherapy Mean(SD)	Mean Difference Fixed, 95% CI	Weight	Mean Difference Fixed, 95% CI
Dobbin 2013	31	9.8 (4.1)	30	9.1 (5.3)		100%	0.7[-1.68,3.08]
Total ***	**31**		**30**			**100%**	**0.7[-1.68,3.08]**
Heterogeneity: Not applicable							
Test for overall effect: Z=0.58(P=0.56)							



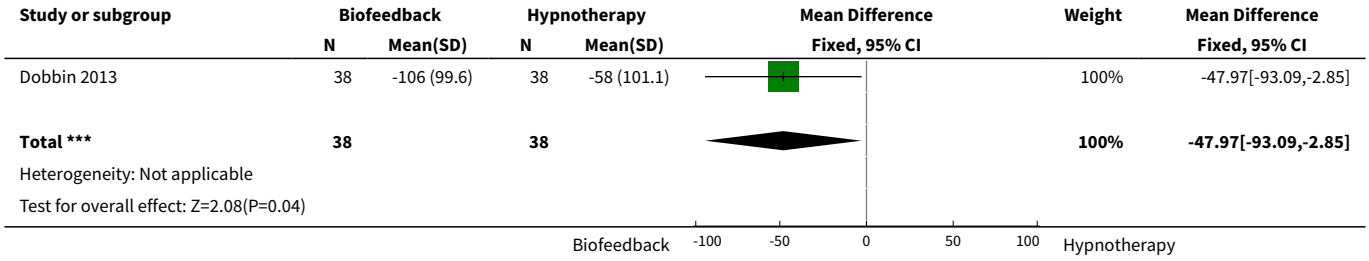
Analysis 3.4. Comparison 3 Biofeedback versus hypnotherapy, Outcome 4 Symptom Improvement (measured by IBS-SSS) - Sensitivity Analysis Strategy 1.

Study or subgroup	Biofeedback N	Biofeedback Mean(SD)	Hypnotherapy N	Hypnotherapy Mean(SD)	Mean Difference Fixed, 95% CI	Weight	Mean Difference Fixed, 95% CI
Dobbin 2013	38	-106 (99.6)	38	-58 (101.1)		100%	-47.97[-93.09,-2.85]
Total ***	**38**		**38**			**100%**	**-47.97[-93.09,-2.85]**
Heterogeneity: Not applicable							
Test for overall effect: Z=2.08(P=0.04)							

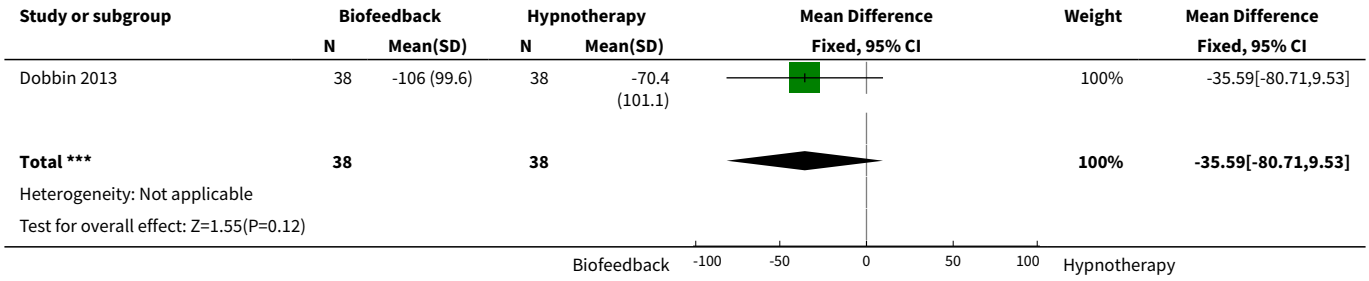
Analysis 3.5. Comparison 3 Biofeedback versus hypnotherapy, Outcome 5 Symptom Improvement (measured by IBS-SSS) - Sensitivity Analysis Strategy 2.



Analysis 3.6. Comparison 3 Biofeedback versus hypnotherapy, Outcome 6 Symptom Improvement (measured by IBS-SSS) - Sensitivity Analysis Strategy 3.



Analysis 3.7. Comparison 3 Biofeedback versus hypnotherapy, Outcome 7 Symptom Improvement (measured by IBS-SSS) - Sensitivity Analysis Strategy 4.

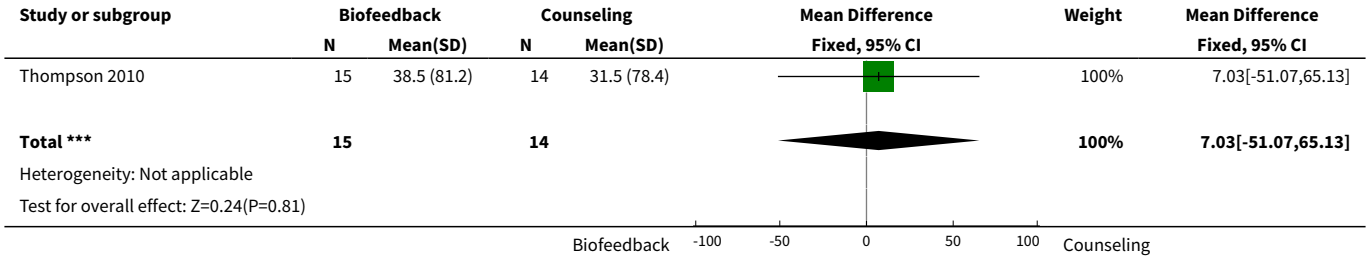


Comparison 4. Biofeedback versus Counseling

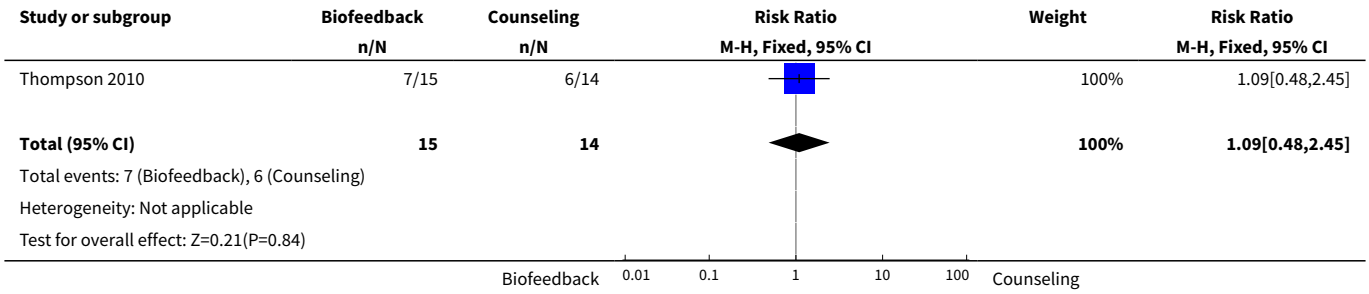
Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Symptom Improvement (measured by CPSR)	1	29	Mean Difference (IV, Fixed, 95% CI)	7.03 [-51.07, 65.13]
2 Clinical Response (complete case)	1	29	Risk Ratio (M-H, Fixed, 95% CI)	1.09 [0.48, 2.45]

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
3 Adverse Events	1	29	Risk Difference (M-H, Fixed, 95% CI)	0.0 [-0.12, 0.12]
4 Serious Adverse Events	1	29	Risk Difference (M-H, Fixed, 95% CI)	0.0 [-0.12, 0.12]
5 Abdominal Pain	1	29	Mean Difference (IV, Fixed, 95% CI)	0.04 [-0.43, 0.52]

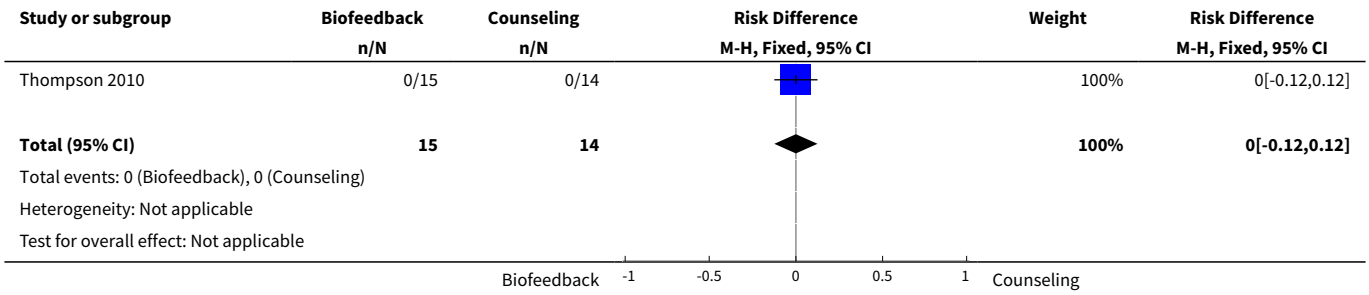
Analysis 4.1. Comparison 4 Biofeedback versus Counseling, Outcome 1 Symptom Improvement (measured by CPSR).



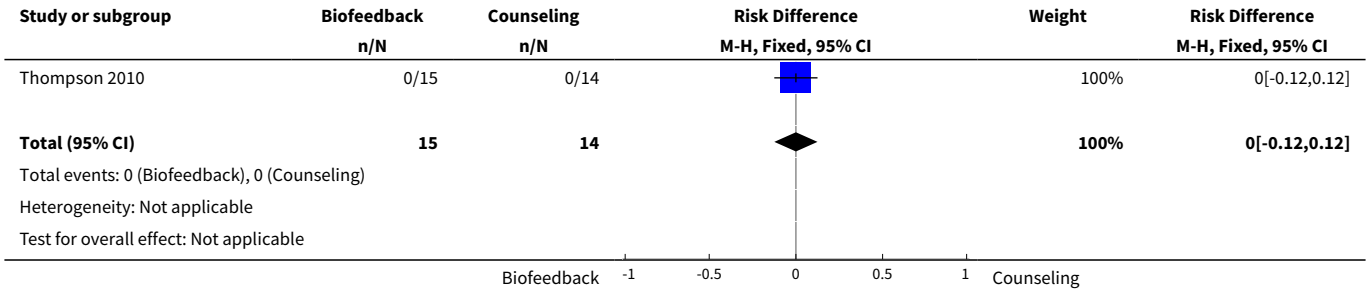
Analysis 4.2. Comparison 4 Biofeedback versus Counseling, Outcome 2 Clinical Response (complete case).



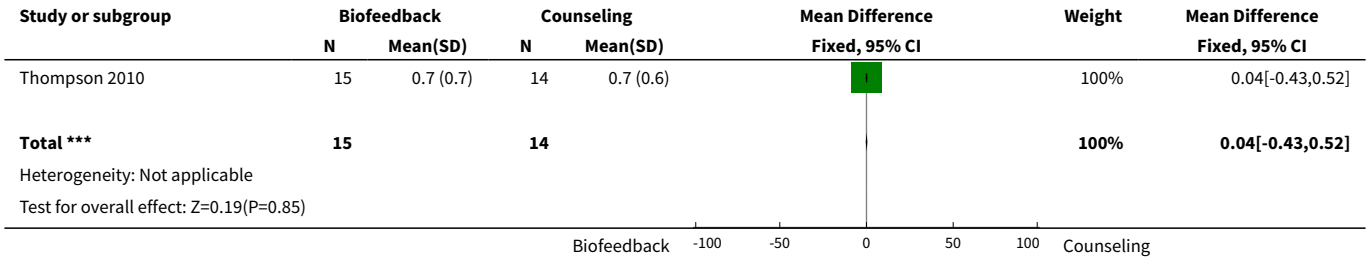
Analysis 4.3. Comparison 4 Biofeedback versus Counseling, Outcome 3 Adverse Events.



Analysis 4.4. Comparison 4 Biofeedback versus Counseling, Outcome 4 Serious Adverse Events.



Analysis 4.5. Comparison 4 Biofeedback versus Counseling, Outcome 5 Abdominal Pain.



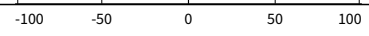
Comparison 5. Multi-component psychological intervention (with biofeedback) versus no-treatment control

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Symptom Improvement (measured by CPSR)	3	101	Mean Difference (IV, Fixed, 95% CI)	30.34 [8.47, 52.21]
2 Symptom Improvement (measured by CPSR) - Sensitivity Analysis - Random Effects	3	101	Mean Difference (IV, Random, 95% CI)	30.34 [8.47, 52.21]
3 Symptom Improvement (measured by CPSR) - Sensitivity Analysis Strategy 1	3	117	Mean Difference (IV, Fixed, 95% CI)	27.02 [6.80, 47.24]
4 Symptom Improvement (measured by CPSR) - Sensitivity Analysis Strategy 2	3	117	Mean Difference (IV, Fixed, 95% CI)	28.75 [8.52, 48.97]
5 Symptom Improvement (measured by CPSR) - Sensitivity Analysis Strategy 3	3	117	Mean Difference (IV, Fixed, 95% CI)	25.94 [5.71, 46.16]
6 Symptom Improvement (measured by CPSR) - Sensitivity Analysis Strategy 4	3	117	Mean Difference (IV, Fixed, 95% CI)	20.85 [0.63, 41.08]
7 Clinical Response (complete case)	3	101	Risk Ratio (M-H, Fixed, 95% CI)	2.12 [1.24, 3.62]
8 Clinical Response - Sensitivity Analysis - Random Effects	3	101	Risk Ratio (M-H, Random, 95% CI)	1.95 [1.14, 3.32]

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
9 Clinical Response -Sensitivity Analysis - Missing Outcome Data - 1.5:1	3	117	Risk Ratio (M-H, Fixed, 95% CI)	1.91 [1.17, 3.13]
10 Clinical Response -Sensitivity Analysis - Missing Outcome Data - 2:1	3	117	Risk Ratio (M-H, Fixed, 95% CI)	1.78 [1.08, 2.95]
11 Abdominal Pain	2	82	Mean Difference (IV, Fixed, 95% CI)	-1.40 [-7.54, 4.74]
12 Depression	2	82	Mean Difference (IV, Fixed, 95% CI)	-3.80 [-6.90, -0.69]
13 Anxiety - State	2	82	Mean Difference (IV, Fixed, 95% CI)	-8.63 [-12.48, -4.77]
14 Anxiety - Trait	2	82	Mean Difference (IV, Fixed, 95% CI)	-3.98 [-7.96, -0.00]

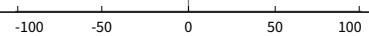
Analysis 5.1. Comparison 5 Multi-component psychological intervention (with biofeedback) versus no-treatment control, Outcome 1 Symptom Improvement (measured by CPSR).

Study or subgroup	MCPI with biofeedback N	MCPI with biofeedback Mean(SD)	no-treatment control N	no-treatment control Mean(SD)	Mean Difference Fixed, 95% CI	Weight	Mean Difference Fixed, 95% CI
Blanchard 1992a	10	45.2 (59.3)	10	9.5 (53.3)		19.59%	35.7[-13.72,85.12]
Blanchard 1992b	31	32.4 (63.2)	31	6.4 (57)		53.3%	26[-3.96,55.96]
Neff 1987	10	50.4 (47.9)	9	15.4 (45.5)		27.11%	35[-7.01,77.01]
Total ***	**51**		**50**			**100%**	**30.34[8.47,52.21]**
Heterogeneity: Tau^2=0; Chi^2=0.17, df=2(P=0.92); I^2=0%							
Test for overall effect: Z=2.72(P=0.01)							



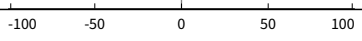
Analysis 5.2. Comparison 5 Multi-component psychological intervention (with biofeedback) versus no-treatment control, Outcome 2 Symptom Improvement (measured by CPSR) - Sensitivity Analysis - Random Effects.

Study or subgroup	MCPI with biofeedback N	MCPI with biofeedback Mean(SD)	no-treatment control N	no-treatment control Mean(SD)	Mean Difference Random, 95% CI	Weight	Mean Difference Random, 95% CI
Blanchard 1992a	10	45.2 (59.3)	10	9.5 (53.3)		19.59%	35.7[-13.72,85.12]
Blanchard 1992b	31	32.4 (63.2)	31	6.4 (57)		53.3%	26[-3.96,55.96]
Neff 1987	10	50.4 (47.9)	9	15.4 (45.5)		27.11%	35[-7.01,77.01]
Total ***	**51**		**50**			**100%**	**30.34[8.47,52.21]**
Heterogeneity: Tau^2=0; Chi^2=0.17, df=2(P=0.92); I^2=0%							
Test for overall effect: Z=2.72(P=0.01)							



Analysis 5.3. Comparison 5 Multi-component psychological intervention (with biofeedback) versus no-treatment control, Outcome 3 Symptom Improvement (measured by CPSR) - Sensitivity Analysis Strategy 1.

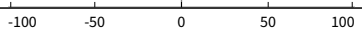
Study or subgroup	MCPI with biofeedback		no-treatment control		Mean Difference	Weight	Mean Difference
	N	Mean(SD)	N	Mean(SD)	Fixed, 95% CI		Fixed, 95% CI
Blanchard 1992a	10	45.2 (60)	10	9.5 (53.3)		16.53%	35.7[-14.05,85.45]
Blanchard 1992b	38	27.6 (61.7)	39	6.4 (56.3)		58.69%	21.21[-5.19,47.61]
Neff 1987	10	50.4 (47.2)	10	15.4 (45.5)		24.78%	35[-5.62,75.62]
Total ***	**58**		**59**			**100%**	**27.02[6.8,47.24]**
Heterogeneity: Tau²=0; Chi²=0.45, df=2(P=0.8); I²=0%							
Test for overall effect: Z=2.62(P=0.01)							



MCPI with biofeedback | no-treatment control

Analysis 5.4. Comparison 5 Multi-component psychological intervention (with biofeedback) versus no-treatment control, Outcome 4 Symptom Improvement (measured by CPSR) - Sensitivity Analysis Strategy 2.

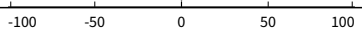
Study or subgroup	MCPI with biofeedback		no-treatment control		Mean Difference	Weight	Mean Difference
	N	Mean(SD)	N	Mean(SD)	Fixed, 95% CI		Fixed, 95% CI
Blanchard 1992a	10	45.2 (60)	10	9.5 (53.3)		16.53%	35.7[-14.05,85.45]
Blanchard 1992b	38	32.4 (61.7)	39	8.3 (56.3)		58.69%	24.15[-2.25,50.55]
Neff 1987	10	50.4 (47.2)	10	15.4 (45.5)		24.78%	35[-5.62,75.62]
Total ***	**58**		**59**			**100%**	**28.75[8.52,48.97]**
Heterogeneity: Tau²=0; Chi²=0.28, df=2(P=0.87); I²=0%							
Test for overall effect: Z=2.79(P=0.01)							



MCPI with biofeedback | no-treatment control

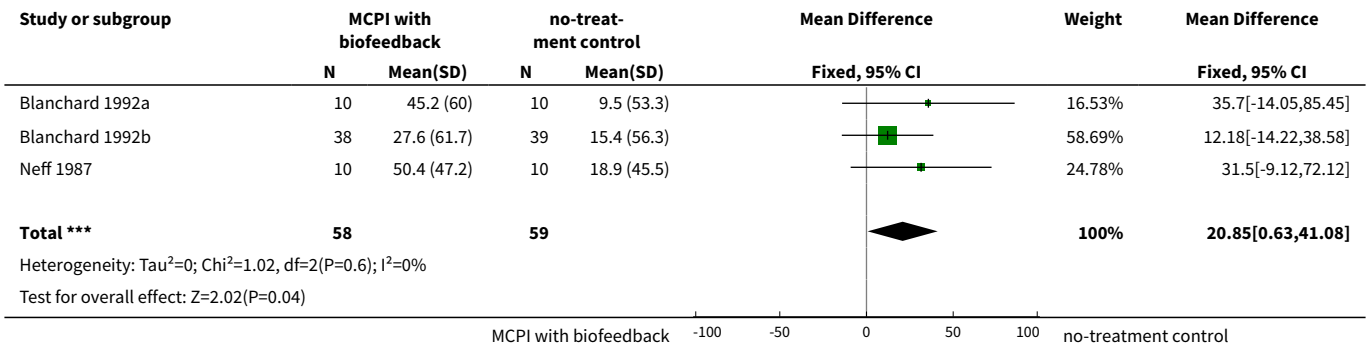
Analysis 5.5. Comparison 5 Multi-component psychological intervention (with biofeedback) versus no-treatment control, Outcome 5 Symptom Improvement (measured by CPSR) - Sensitivity Analysis Strategy 3.

Study or subgroup	MCPI with biofeedback		no-treatment control		Mean Difference	Weight	Mean Difference
	N	Mean(SD)	N	Mean(SD)	Fixed, 95% CI		Fixed, 95% CI
Blanchard 1992a	10	45.2 (60)	10	9.5 (53.3)		16.53%	35.7[-14.05,85.45]
Blanchard 1992b	38	27.6 (61.7)	39	8.3 (56.3)		58.69%	19.36[-7.04,45.76]
Neff 1987	10	50.4 (47.2)	10	15.4 (45.5)		24.78%	35[-5.62,75.62]
Total ***	**58**		**59**			**100%**	**25.94[5.71,46.16]**
Heterogeneity: Tau²=0; Chi²=0.58, df=2(P=0.75); I²=0%							
Test for overall effect: Z=2.51(P=0.01)							

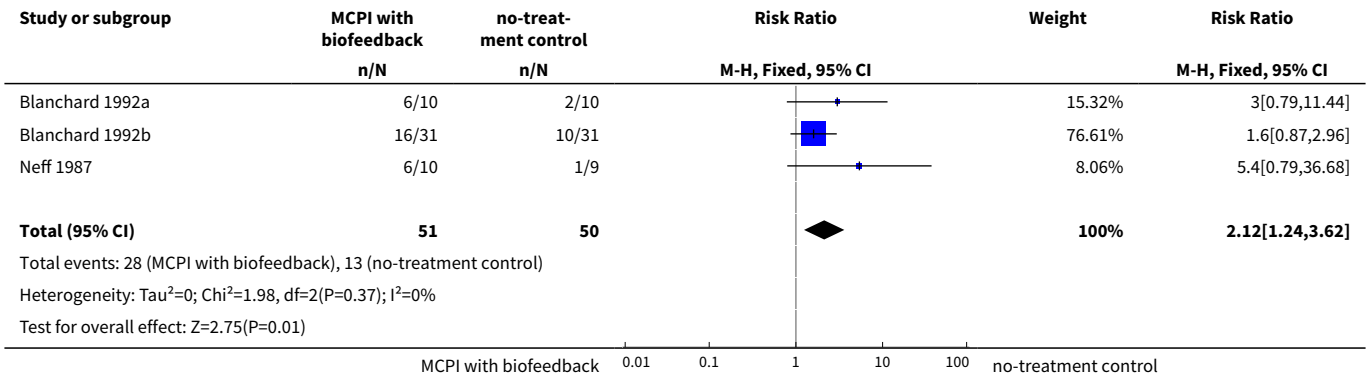


MCPI with biofeedback | no-treatment control

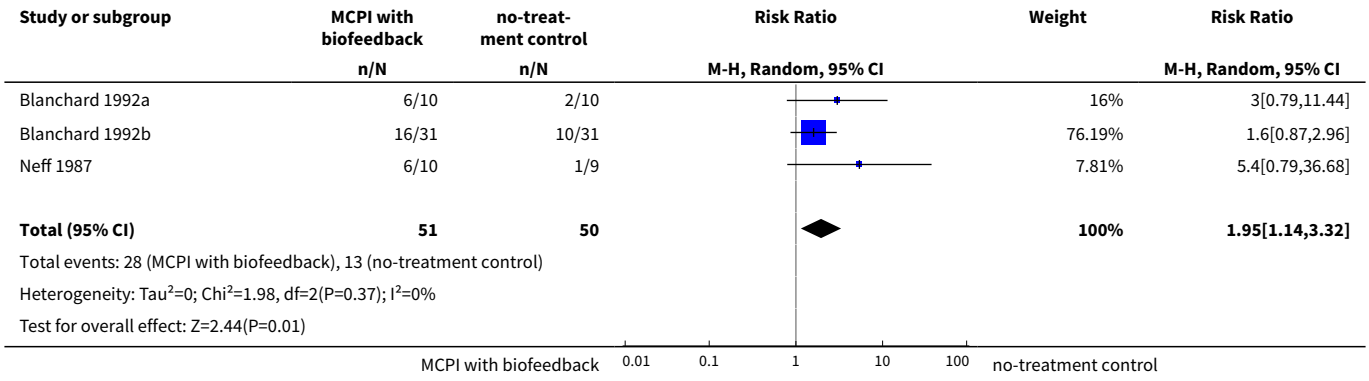
Analysis 5.6. Comparison 5 Multi-component psychological intervention (with biofeedback) versus no-treatment control, Outcome 6 Symptom Improvement (measured by CPSR) - Sensitivity Analysis Strategy 4.



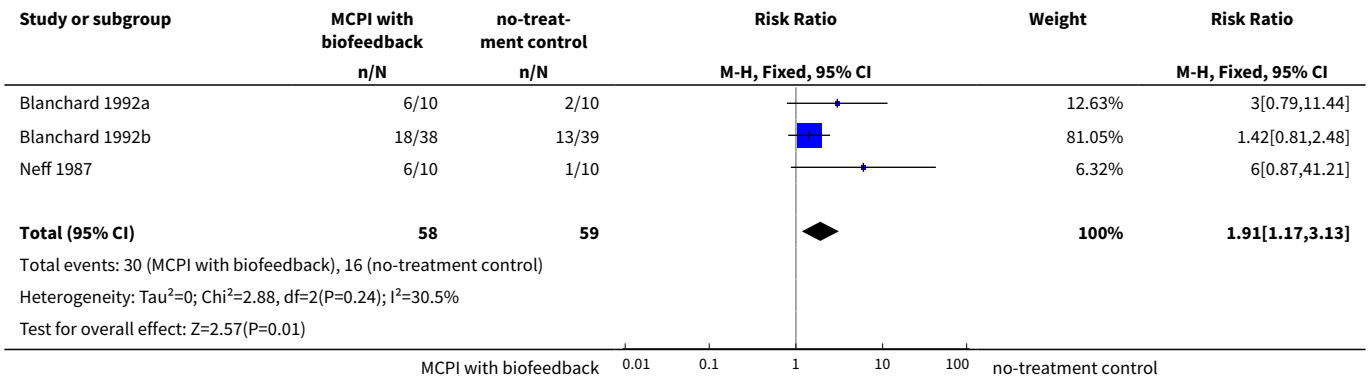
Analysis 5.7. Comparison 5 Multi-component psychological intervention (with biofeedback) versus no-treatment control, Outcome 7 Clinical Response (complete case).



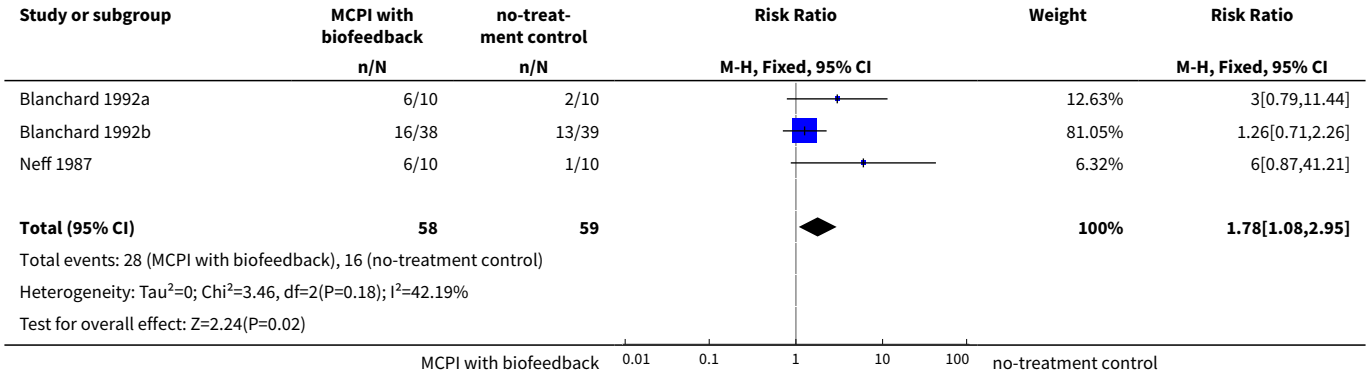
Analysis 5.8. Comparison 5 Multi-component psychological intervention (with biofeedback) versus no-treatment control, Outcome 8 Clinical Response - Sensitivity Analysis - Random Effects.



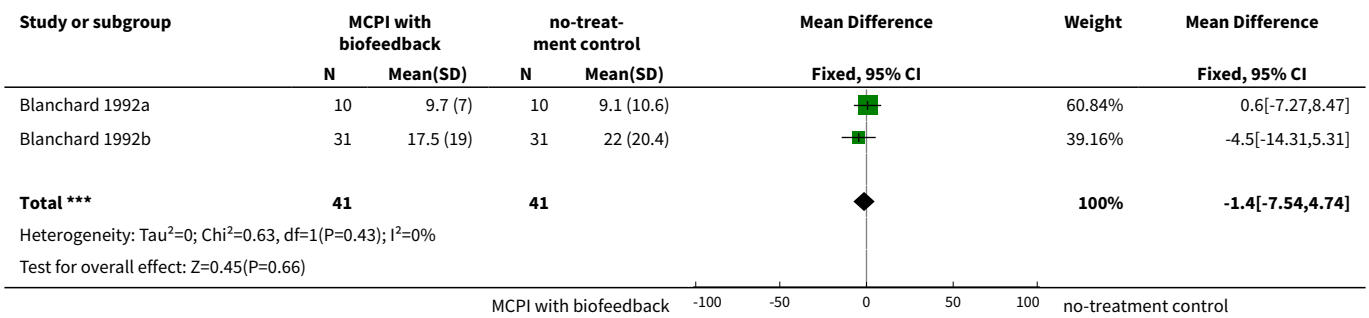
Analysis 5.9. Comparison 5 Multi-component psychological intervention (with biofeedback) versus no-treatment control, Outcome 9 Clinical Response -Sensitivity Analysis - Missing Outcome Data - 1.5:1.



Analysis 5.10. Comparison 5 Multi-component psychological intervention (with biofeedback) versus no-treatment control, Outcome 10 Clinical Response -Sensitivity Analysis - Missing Outcome Data - 2:1.

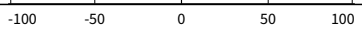


Analysis 5.11. Comparison 5 Multi-component psychological intervention (with biofeedback) versus no-treatment control, Outcome 11 Abdominal Pain.



Analysis 5.12. Comparison 5 Multi-component psychological intervention (with biofeedback) versus no-treatment control, Outcome 12 Depression.

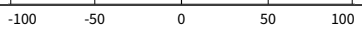
Study or subgroup	MCPI with biofeedback N	MCPI with biofeedback Mean(SD)	no-treatment control N	no-treatment control Mean(SD)	Mean Difference Fixed, 95% CI	Weight	Mean Difference Fixed, 95% CI
Blanchard 1992a	10	8.4 (5.3)	10	11.7 (10.9)		17.09%	-3.3[-10.81,4.21]
Blanchard 1992b	31	6.6 (6.7)	31	10.5 (7)		82.91%	-3.9[-7.31,-0.49]
Total ***	**41**		**41**			**100%**	**-3.8[-6.9,-0.69]**
Heterogeneity: Tau^2=0; Chi^2=0.02, df=1(P=0.89); I^2=0%							
Test for overall effect: Z=2.4(P=0.02)							



MCPI with biofeedback | no-treatment control

Analysis 5.13. Comparison 5 Multi-component psychological intervention (with biofeedback) versus no-treatment control, Outcome 13 Anxiety - State.

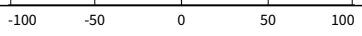
Study or subgroup	MCPI with biofeedback N	MCPI with biofeedback Mean(SD)	no-treatment control N	no-treatment control Mean(SD)	Mean Difference Fixed, 95% CI	Weight	Mean Difference Fixed, 95% CI
Blanchard 1992a	10	33.3 (10.3)	10	42.2 (18.6)		8.54%	-8.9[-22.08,4.28]
Blanchard 1992b	31	35.9 (9.2)	31	44.5 (6.8)		91.46%	-8.6[-12.63,-4.57]
Total ***	**41**		**41**			**100%**	**-8.63[-12.48,-4.77]**
Heterogeneity: Tau^2=0; Chi^2=0, df=1(P=0.97); I^2=0%							
Test for overall effect: Z=4.39(P<0.0001)							



MCPI with biofeedback | no-treatment control

Analysis 5.14. Comparison 5 Multi-component psychological intervention (with biofeedback) versus no-treatment control, Outcome 14 Anxiety - Trait.

Study or subgroup	MCPI with biofeedback N	MCPI with biofeedback Mean(SD)	no-treatment control N	no-treatment control Mean(SD)	Mean Difference Fixed, 95% CI	Weight	Mean Difference Fixed, 95% CI
Blanchard 1992a	10	37.9 (7.6)	10	48.5 (14)		16.23%	-10.6[-20.47,-0.73]
Blanchard 1992b	31	43.8 (9.4)	31	46.5 (8)		83.77%	-2.7[-7.05,1.65]
Total ***	**41**		**41**			**100%**	**-3.98[-7.96,-0]**
Heterogeneity: Tau^2=0; Chi^2=2.06, df=1(P=0.15); I^2=51.46%							
Test for overall effect: Z=1.96(P=0.05)							



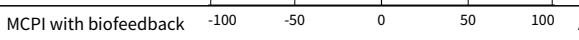
MCPI with biofeedback | no-treatment control

Comparison 6. Multi-component psychological intervention (with biofeedback) versus attention control

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Symptom Improvement (measured by CPSR)	2	80	Mean Difference (IV, Fixed, 95% CI)	4.02 [-21.41, 29.45]
2 Clinical Response (complete case)	2	80	Risk Ratio (M-H, Fixed, 95% CI)	1.10 [0.72, 1.69]
3 Abdominal Pain	2	80	Mean Difference (IV, Fixed, 95% CI)	0.72 [-5.40, 6.84]
4 Depression	2	80	Mean Difference (IV, Fixed, 95% CI)	0.13 [-2.73, 2.98]
5 Anxiety - State	2	80	Mean Difference (IV, Fixed, 95% CI)	-0.74 [-5.38, 3.89]
6 Anxiety - Trait	2	80	Mean Difference (IV, Fixed, 95% CI)	2.05 [-2.48, 6.57]

Analysis 6.1. Comparison 6 Multi-component psychological intervention (with biofeedback) versus attention control, Outcome 1 Symptom Improvement (measured by CPSR).

Study or subgroup	MCPI with biofeedback N	MCPI with biofeedback Mean(SD)	Attention control N	Attention control Mean(SD)	Mean Difference Fixed, 95% CI	Weight	Mean Difference Fixed, 95% CI
Blanchard 1992a	10	45.2 (59.3)	9	38 (31.6)		36.38%	7.2[-34.96,49.36]
Blanchard 1992b	31	32.4 (63.2)	30	30.2 (63.8)		63.62%	2.2[-29.68,34.08]
Total ***	**41**		**39**			**100%**	**4.02[-21.41,29.45]**
Heterogeneity: Tau²=0; Chi²=0.03, df=1(P=0.85); I²=0%							
Test for overall effect: Z=0.31(P=0.76)							

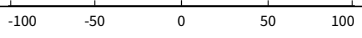


Analysis 6.2. Comparison 6 Multi-component psychological intervention (with biofeedback) versus attention control, Outcome 2 Clinical Response (complete case).

Study or subgroup	MCPI with biofeedback n/N	Attention control n/N	Risk Ratio M-H, Fixed, 95% CI	Weight	Risk Ratio M-H, Fixed, 95% CI
Blanchard 1992a	6/10	5/9		27%	1.08[0.5,2.34]
Blanchard 1992b	16/31	14/30		73%	1.11[0.66,1.85]
Total (95% CI)	**41**	**39**		**100%**	**1.1[0.72,1.69]**
Total events: 22 (MCPI with biofeedback), 19 (Attention control)					
Heterogeneity: Tau²=0; Chi²=0, df=1(P=0.96); I²=0%					
Test for overall effect: Z=0.43(P=0.67)					

Analysis 6.3. Comparison 6 Multi-component psychological intervention (with biofeedback) versus attention control, Outcome 3 Abdominal Pain.

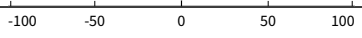
Study or subgroup	MCPI with biofeedback		Attention control		Mean Difference	Weight	Mean Difference
	N	Mean(SD)	N	Mean(SD)	Fixed, 95% CI		Fixed, 95% CI
Blanchard 1992a	10	9.7 (7)	9	11.7 (10.8)		54.63%	-2[-10.28,6.28]
Blanchard 1992b	31	17.5 (19)	30	13.5 (17.2)		45.37%	4[-5.09,13.09]
Total ***	**41**		**39**			**100%**	**0.72[-5.4,6.84]**
Heterogeneity: Tau^2=0; Chi^2=0.91, df=1(P=0.34); I^2=0%							
Test for overall effect: Z=0.23(P=0.82)							



MCPI with biofeedback — Attention control

Analysis 6.4. Comparison 6 Multi-component psychological intervention (with biofeedback) versus attention control, Outcome 4 Depression.

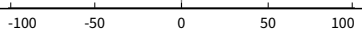
Study or subgroup	MCPI with biofeedback		Attention control		Mean Difference	Weight	Mean Difference
	N	Mean(SD)	N	Mean(SD)	Fixed, 95% CI		Fixed, 95% CI
Blanchard 1992a	10	8.4 (5.3)	9	7.9 (5)		38%	0.5[-4.13,5.13]
Blanchard 1992b	31	6.6 (6.7)	30	6.7 (7.7)		62%	-0.1[-3.73,3.53]
Total ***	**41**		**39**			**100%**	**0.13[-2.73,2.98]**
Heterogeneity: Tau^2=0; Chi^2=0.04, df=1(P=0.84); I^2=0%							
Test for overall effect: Z=0.09(P=0.93)							



MCPI with biofeedback — Attention control

Analysis 6.5. Comparison 6 Multi-component psychological intervention (with biofeedback) versus attention control, Outcome 5 Anxiety - State.

Study or subgroup	MCPI with biofeedback		Attention control		Mean Difference	Weight	Mean Difference
	N	Mean(SD)	N	Mean(SD)	Fixed, 95% CI		Fixed, 95% CI
Blanchard 1992a	10	33.3 (10.3)	9	36.3 (14.5)		16.45%	-3[-14.42,8.42]
Blanchard 1992b	31	35.9 (9.2)	30	36.2 (10.9)		83.55%	-0.3[-5.37,4.77]
Total ***	**41**		**39**			**100%**	**-0.74[-5.38,3.89]**
Heterogeneity: Tau^2=0; Chi^2=0.18, df=1(P=0.67); I^2=0%							
Test for overall effect: Z=0.31(P=0.75)							



MCPI with biofeedback — Attention control

Analysis 6.6. Comparison 6 Multi-component psychological intervention (with biofeedback) versus attention control, Outcome 6 Anxiety - Trait.

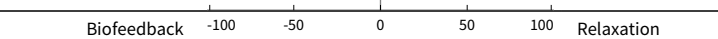
Study or subgroup	MCPI with biofeedback		Attention control		Mean Difference	Weight	Mean Difference
	N	Mean(SD)	N	Mean(SD)	Fixed, 95% CI		Fixed, 95% CI
Blanchard 1992a	10	37.9 (7.6)	9	40.8 (10.3)		30.34%	-2.9[-11.11,5.31]
Blanchard 1992b	31	43.8 (9.4)	30	39.6 (12)		69.66%	4.2[-1.22,9.62]
Total ***	**41**		**39**			**100%**	**2.05[-2.48,6.57]**
Heterogeneity: Tau^2=0; Chi^2=2, df=1(P=0.16); I^2=49.98%							
Test for overall effect: Z=0.89(P=0.38)							

Comparison 7. Biofeedback versus relaxation control

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Symptom severity	1	10	Mean Difference (IV, Fixed, 95% CI)	0.0 [0.0, 0.0]
2 Stool frequency	0	0	Mean Difference (IV, Fixed, 95% CI)	0.0 [0.0, 0.0]
3 Abdominal pain	0	0	Mean Difference (IV, Fixed, 95% CI)	0.0 [0.0, 0.0]
4 Depression	0	0	Mean Difference (IV, Fixed, 95% CI)	0.0 [0.0, 0.0]
5 Anxiety	0	0	Mean Difference (IV, Fixed, 95% CI)	0.0 [0.0, 0.0]

Analysis 7.1. Comparison 7 Biofeedback versus relaxation control, Outcome 1 Symptom severity.

Study or subgroup	Biofeedback		Relaxation		Mean Difference	Weight	Mean Difference
	N	Mean(SD)	N	Mean(SD)	Fixed, 95% CI		Fixed, 95% CI
DeRoo 1988	5	2.8 (0)	5	2.5 (0)			Not estimable
Total ***	**5**		**5**				**Not estimable**
Heterogeneity: Not applicable							
Test for overall effect: Not applicable							



APPENDICES

Appendix 1. Database search strategies

MEDLINE

#1 Irritable bowel syndrome[mh]

#2 Colonic Diseases, Functional[mh]

#3 “irritable bowel syndrome”[tw]

#4 irritable bowel syndrome*[tw]

#5 IBS[tw]

#6 “functional abdominal pain”[tw]

#7 “functional gastrointestinal disorders”[tw]

#8 #1 OR #2 OR #3 OR #4 OR #5 OR #6 OR #7

#9 recurrent[tw]

#10 chronic[tw]

#11 excessive[tw]

#12 hypersensitivity[tw]

#13 #9 OR #10 OR #11 OR #12

#14 diarrhea*[tw]

#15 diarrhoe*[tw]

#16 diarhe*[tw]

#17 diarhoe*[tw]

#18 "gastro enteritis”[tw]

#19 "abdominal pain”[tw]

#20 abdominal cramp*[tw]

#21 bloating[tw]

#22 "disturbed defecation”[tw]

#23 constipat*[tw]

#24 flatulen*[tw]

#25 #14 OR #15 OR #16 OR #17 OR #18 OR #19 OR #20 OR #21 OR #22 OR #23 OR #24

#26 #13 AND #25

#27 #8 OR #26

#28 Biofeedback, Psychology[mh]

#29 Neurofeedback[mh]

#30 Electroencephalography[mh]

#31 Electromyography[mh]

#32 Monitoring, Physiologic[mh]

#33 Thermography[mh]

#34 Hypnosis[mh]

#35 Relaxation Therapy[mh]

#36 Yoga[mh]

#37 Mindfulness[mh]

#38 Mediation[mh]

#39 biofeed*[tw]

#40 myofeedback[tw]

#41 neurobiofeedback[tw]

#42 neurofeed*[tw]

#43 neurotherap*[tw]

#44 electroencephalograp*[tw]

#45 EEG[tw]

#46 electromyograph*[tw]

#47 EMG[tw]

#48 thermistor*[tw]

#49 hypnosis[tw]

#50 hypnotherap*[tw]

#51 “gut directed hypnotherapy”[tw]

#52 “relaxation training”[tw]

#53 "progressive muscle relaxation"[tw]

#54 “progressive relaxation”[tw]

#55 yoga*[tw]

#56 mindful*[tw]

#57 meditati*[tw]

#58 EmWAVE[tw]

#59 heart rate vari*[tw]

#60 HRV

#61 #28 OR #29 OR #30 OR #31 OR #32 OR #33 OR #34 OR #35 OR #36 OR #37 OR #38 OR #39 OR #40 OR #41 OR #42 OR #43 OR #44 OR #45 OR #46 OR #47 OR #48 OR #49 OR #50 OR #51 OR #52 OR #53 OR #54 OR #55 OR #56 OR #57 OR #58 OR #59 OR #60

#62 randomized controlled trial [pt]

#63 controlled clinical trial [pt]

#64 randomized [tiab]

#65 placebo [tiab]

#66 drug therapy [sh]

#67 randomly [tiab]

#68 trial [tiab]

#69 groups [tiab]

#70 #62 OR #63 OR #64 OR #65 OR #66 OR #67 OR #68 OR #69

#71 animals [mh]

#72 humans [mh]

#73 #71 AND #72

#74 #71 NOT #73

#75 #27 AND #61 AND #70

#76 #75 NOT #74

Cochrane Central Register of Controlled Trials (CENTRAL)

#1 MeSH descriptor: [Irritable Bowel Syndrome] explode all trees

#2 MeSH descriptor: [Colonic Diseases, Functional] explode all trees

#3 "irritable bowel syndrome":ti,ab,kw (Word variations have been searched)

#4 irritable bowel syndrome*:ti,ab,kw (Word variations have been searched)

#5 IBS:ti,ab,kw (Word variations have been searched)

#6 "functional abdominal pain":ti,ab,kw (Word variations have been searched)

#7 "functional gastrointestinal disorders":ti,ab,kw (Word variations have been searched)

#8 #1 or #2 or #3 or #4 or #5 or #6 or #7

#9 recurrent:ti,ab,kw (Word variations have been searched)

#10 chronic:ti,ab,kw (Word variations have been searched)

#11 excessive:ti,ab,kw (Word variations have been searched)

#12 hypersensitivity:ti,ab,kw (Word variations have been searched)

#13 #9 or #10 or #11 or #12

#14 diarrhea*:ti,ab,kw (Word variations have been searched)

#15 diarrhoe*:ti,ab,kw (Word variations have been searched)

#16 diarhe*:ti,ab,kw (Word variations have been searched)

#17 diarhoe*:ti,ab,kw (Word variations have been searched)

#18 "gastro enteritis":ti,ab,kw (Word variations have been searched)

#19 "abdominal pain":ti,ab,kw (Word variations have been searched)

#20 abdominal cramp*:ti,ab,kw (Word variations have been searched)

#21 bloating:ti,ab,kw (Word variations have been searched)

#22 "disturbed defecation":ti,ab,kw (Word variations have been searched)

#23 constipat*:ti,ab,kw (Word variations have been searched)

#24 flatulen*:ti,ab,kw (Word variations have been searched)

#25 #14 or #15 or #16 or #17 or #18 or #19 or #20 or #21 or #22 or #23 or #24

#26 #13 and #25

#27 #8 or #26

#28 MeSH descriptor: [Biofeedback, Psychology] explode all trees

#29 MeSH descriptor: [Neurofeedback] explode all trees

#30 MeSH descriptor: [Electroencephalography] explode all trees

#31 MeSH descriptor: [Electromyography] explode all trees

#32 MeSH descriptor: [Monitoring, Physiologic] explode all trees

#33 MeSH descriptor: [Thermography] explode all trees

#34 MeSH descriptor: [Hypnosis] explode all trees

#35 MeSH descriptor: [Relaxation Therapy] explode all trees

#36 MeSH descriptor: [Yoga] explode all trees

#37 MeSH descriptor: [Mindfulness] explode all trees

#38 MeSH descriptor: [Meditation] explode all trees

#39 biofeed*:ti,ab,kw (Word variations have been searched)

#40 myofeedback:ti,ab,kw (Word variations have been searched)

#41 neurobiofeedback:ti,ab,kw (Word variations have been searched)

#42 neurofeed*:ti,ab,kw (Word variations have been searched)

#43 neurotherap*:ti,ab,kw (Word variations have been searched)

#44 electroencephalograp*:ti,ab,kw (Word variations have been searched)

#45 EEG:ti,ab,kw (Word variations have been searched)

#46 electromyograph*:ti,ab,kw (Word variations have been searched)

#47 EMG:ti,ab,kw (Word variations have been searched)

#48 thermistor*:ti,ab,kw (Word variations have been searched)

#49 hypnosis:ti,ab,kw (Word variations have been searched)

#50 hypnotherap*:ti,ab,kw (Word variations have been searched)

#51 "gut directed hypnotherapy":ti,ab,kw (Word variations have been searched)

#52 "relaxation training":ti,ab,kw (Word variations have been searched)

#53 "progressive muscle relaxation":ti,ab,kw (Word variations have been searched)

#54 "progressive relaxation":ti,ab,kw (Word variations have been searched)

#55 yoga*:ti,ab,kw (Word variations have been searched)

#56 mindful*:ti,ab,kw (Word variations have been searched)

#57 meditati*:ti,ab,kw (Word variations have been searched)

#58 EmWAVE:ti,ab,kw (Word variations have been searched)

#59 heart rate vari*:ti,ab,kw (Word variations have been searched)

#60 HRV:ti,ab,kw (Word variations have been searched)

#61 #28 or #29 or #30 or #31 or #32 or #33 or #34 or #35 or #36 or #37 or #38 or #39 or #40 or #41 or #42 or #43 or #44 or #45 or #46 or #47 or #48 or #49 or #50 or #51 or #52 or #53 or #54 or #55 or #56 or #57 or #58 or #59 or #60

#62 MeSH descriptor: [Animals] explode all trees

#63 MeSH descriptor: [Humans] explode all trees

#64 #62 and #63

#65 #62 not #64

#66 #27 and #61

#67 #66 not #65

Embase

#1 ('intestine function disorder'/exp OR 'irritable colon' OR 'irritable bowel syndrome*' OR IBS OR 'functional gastrointestinal disorder*' OR 'functional abdominal pain')

#2 (recurrent OR chronic OR excessive OR hypersensitivity) AND ('diarrhea'/exp OR 'gastroenteritis'/exp OR 'abdominal cramp'/exp OR 'abdominal pain'/exp OR 'bloating'/exp OR 'constipation'/exp OR 'flatulence'/exp OR 'diarrhea*' OR 'diarrhoe*' OR 'diarhe*' OR 'diarhoe*' OR 'gastro enteritis' OR 'abdominal cramp*' OR 'abdominal pain*' OR bloating OR 'constipat*' OR 'flatulen*' OR 'disturbed defecation')

#3 1 OR 2

#4 ('feedback system'/exp OR 'neurofeedback'/exp OR 'electroencephalography'/exp OR 'electromyography'/exp OR 'physiologic monitoring'/exp OR 'thermography'/exp OR 'thermistor'/exp OR 'hypnosis'/exp OR 'relaxation training'/exp OR 'yoga'/exp OR 'mindfulness'/exp OR 'meditation'/exp OR 'feedback system' OR 'biofeed*' OR 'neurofeed*' OR myofeedback OR neurobiofeedback OR 'neurotherap*' OR 'electroencephalograp*' OR EEG OR 'electromyograph*' OR EMG OR thermistor OR hypnosis OR 'hypnotherap*' OR 'gut directed hypnotherapy' OR 'relaxation therap*' OR 'relaxation training' OR 'progressive muscle relaxation' OR 'progressive relaxation' OR 'yoga*' OR 'mindful*' OR 'meditati*' OR EmWAVE OR 'heart rate vari*' OR HRV)

#5 (random:ti,ab OR placebo:ti,ab OR double-blind:ti,ab)

#6 3 AND 4 AND 5

CINAHL Complete

((MH "Irritable bowel syndrome+") OR (MH "Colonic Diseases, Functional+") OR "irritable bowel syndrome" OR Irritable bowel syndrome* OR IBS OR "Functional abdominal pain" OR "functional gastrointestinal disorder*") OR ((recurrent OR chronic OR excessive OR hypersensitivity) AND (diarrhea* OR diarrhoe* OR diarhe* OR diarhoe* OR "gastro enteritis" OR "abdominal pain" OR abdominal cramp* OR bloating OR "disturbed defecation" OR constipat* OR flatulen*))

AND

((MH "Biofeedback, Psychology+") OR (MH "Neurofeedback+") OR (MH "Electroencephalography+") OR (MH "Electromyography+") OR (MH "Monitoring, Physiologic+") OR (MH "Thermography+") OR (MH "Hypnosis+") OR (MH "Relaxation Therapy+") OR (MH "Yoga+") OR (MH "Mindfulness+") OR (MH "Meditation+") OR biofeed* OR myofeedback OR neurobiofeedback OR neurofeed* OR neurotherap* OR electroencephalograp* OR EEG OR electromyograph* OR EMG OR thermistor* OR hypnosis OR hypnotherap* OR "gut directed hypnotherapy" OR "relaxation training" OR "progressive muscle relaxation" OR "progressive relaxation" OR yoga* OR mindful* OR meditati* OR EmWAVE OR heart rate vari* OR HRV))

AND

((PT "randomized controlled trial") OR (PT "clinical trial") OR (AB "randomized") OR (TI "randomized") OR (AB "trial*") OR (TI "trial*") OR (AB "placebo") OR (TI "placebo") OR (AB "randomly") OR (TI "randomly") OR (AB "trial") OR (TI "trial") OR (AB "groups") OR (TI "groups"))

NOT

((MH "animals+") NOT (MH "humans+"))

The Allied and Complementary Medicine Database (AMED)

#1"Irritable bowel syndrome"

#2 Colonic Diseases, Functional

#3 irritable bowel syndrome*

#4 IBS

#5 "Functional abdominal pain"

#6 "functional gastrointestinal disorders"

#7 #1 OR #2 OR #3 OR #4 OR #5 OR #6

#8 recurrent

#9 chronic

#10 excessive

#11 hypersensitivity

#12 #8 OR #9 OR #10 OR #11

#13 diarrhea*

#14 diarrhoe*

#15 diarhe*

#16 diarhoe

#17 “gastro enteritis”

#18 "abdominal pain"

#19 abdominal cramp*

#20 bloating

#21 "disturbed defecation"

#22 constipat*

#23 flatulen*

#24 #13 OR #14 OR #15 OR #16 OR #17 OR #18 OR #19 OR #20 OR #21 OR #22 OR #23#25 #12 AND #24#26 #7 OR #25

#27 “Physiologic Monitoring”

#28 Thermography

#29 Hypnosis

#30 “Relaxation Therapy”

#31 yoga*

#32 mindful*

#33 meditati*

#34 biofeed*

#35 myofeedback

#36 neurobiofeedback

#37 neurofeed*

#38 neurotherap*

#39 electroencephalograp*

#40 EEG

#41 electromyograph*

#42 EMG

#43 thermistor*

#44 hypnotherap*

#45 “gut directed hypnotherapy”

#46 “relaxation training”

#47 "progressive muscle relaxation"

#48 “progressive relaxation”

#49 EmWAVE

#50 heart rate vari*

#51 HRV

#52 #27 OR #28 OR #29 OR #30 OR #31 OR #32 OR #33 OR #34 OR #35 OR #36 OR #37 OR #38 OR #39 OR #40 OR #41 OR #42 OR #43 OR #44 OR #45 OR #46 OR #47 OR #48 OR #49 OR #50 OR #51

#53 #26 AND #52

Appendix 2. Assessment of heterogeneity

We planned to follow the proposed 13 recommendations for assessing and investigating clinical heterogeneity in systematic reviews (Gagnier 2013). While not all were relevant due to limited identified studies, we describe below how we had planned to apply these recommendations in our review.

1. Review team: we have built a team with both clinical experience in biofeedback and irritable bowel syndrome (IBS), as well as methodological experience in randomized controlled trial (RCT) design, systematic reviews, and meta-analyses.
2. Planning
   a. Our a priori variables to consider in clinical heterogeneity investigation included: type of biofeedback (e.g. heart rate variability), subtype of IBS (i.e. IBS constipation predominant [IBS-C], diarrhea predominant [IBS-D], or mixed [IBS-M]), and diagnostic criteria (e.g. Manning, Rome I-IV).
   b. Any post hoc investigations were to be driven by visual inspection of forest plots.
   c. Investigations were to utilize subgroup analysis or meta-regression as appropriate, subjected to the proposed checklist of subgroup believability (Sun 2012).
   d. Heterogeneity exploration was to be viewed as hypothesis generating.
3. Rationale: our rationale for our a priori variable choice of biofeedback type, IBS subtype, and diagnostic criteria follow our clinical experience as well as recent research suggesting differing mechanisms for IBS-C and IBS-D (Kim 2017). Ad hoc variable choices were to follow pathology, clinical evidence or clinical experience. All variables were to be subject to the proposed checklist of subgroup believability (Sun 2012).
4. Types of variables: all variables used were to be based on the patient, intervention, outcome, or 'other' level as described by Gagnier 2013.
5. Role of statistical heterogeneity: statistical tests such as the Chi^2 and I^2 statistics were to be utilized to help explore heterogeneity but formal statistical tests would not dictate heterogeneity investigation for numerous reasons, including that they are often underpowered as per the recommendations of the heterogeneity Delphi group (Gagnier 2013).
6. Plotting and visual aids: we were to use forest plots as a visual aid in investigating heterogeneity.
7. Dealing with outliers: in the case of clear outliers we were to conduct a sensitivity analysis by removing the outlier trial and comparing the new meta-analytic result to the result before removal.
8. Number of investigations to explore: we followed the principle of parsimony in our variable exploration. We have chosen only three a priori variables.
9. Individual versus aggregate data: this review will utilize aggregate level data only, with the recognition that this approach is liable to ecological bias for patient-level variables. If appropriate these limitations were to be discussed in our discussion.
10. Evidence synthesis: in the case that trials are not reasonably combinable, we were to utilize a narrative synthesis (Popay 2006). We did not pool mixed modality intervention trials (i.e. biofeedback plus A versus control) together with biofeedback alone intervention trials (i.e. biofeedback versus control). We did not combine trials which utilize differing control types (e.g. active, no treatment, and sham).
11. Statistical methods: subgroup analyses were to be utilized as appropriate using RevMan and tests of interaction by the review team. If meta-regression was called for, we were to utilize R based statistical packages and consult with a statistician familiar with this methodology.
12. Interpretation of findings: we were to view our heterogeneity investigations as hypothesis generating, express our confidence in the validity of the findings, and suggest specifically how future research could benefit the evidence base.

13.Reporting:
   a. we attempted to contact study authors for unreported data on the heterogeneity variables we are exploring (e.g. IBS subtype).
   b. we were to report all variables used for heterogeneity exploration.

CONTRIBUTIONS OF AUTHORS

JZG - Conception and design of study, analysis and interpretation of data. Drafting and critical review of the manuscript. Administrative support.

MB - Conception and design of study, analysis and interpretation of data. Drafting and critical review of the manuscript.

JH - Analysis and interpretation of data. Critical review of the manuscript.

MH - Analysis and interpretation of data. Critical review of the manuscript.

JB - Search strategy design. Drafting and critical review of the manuscript.

BL - Study design. Content expert. Critical review of the manuscript.

BCJ - Analysis and critical review of the manuscript

RB - Analysis and interpretation of data. Drafting and critical review of the manuscript.

DECLARATIONS OF INTEREST

Joshua Z Goldenberg: none known

Matthew Brignall: none known

Michelle Hamilton: none known

Jennifer Beardsley: none known

Brad Lichtenstein: none known

Jason Hawrelak: none known

Bradley Johnston: none known

Richard Batson: none known

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