

Best Evidence Summaries of Topics in Mental Healthcare

BEST in MH *clinical question-answering service*

Question

For adults of working age engaged in psychological therapies, what impact does concurrent Benzodiazepine use have on the effectiveness of the intervention?

Clarification of question using the *PRO* structure

Patients: Adults of working age
Intervention: Psychological therapy with concurrent Benzodiazepine use
Comparator: Psychological therapy without concurrent Benzodiazepine use
Outcome: Effectiveness of psychological therapy

Clinical and research implications

No definite clinical implications can be made based on the available evidence. The limited evidence suggested similar outcomes for those randomised to psychotherapy plus benzodiazepines versus those randomised to psychotherapy alone- but the results may not be reliable or generalisable. The authors of a systematic review suggested that, based on the limited evidence, behaviour therapy alongside benzodiazepine use may be better than behaviour therapy alone for panic disorder with agoraphobia during the acute phase, but afterwards this trend may be reversed. The authors also stated that more high-quality trials for combined benzodiazepine and psychotherapy treatment must be conducted before stronger treatment recommendations can be made.

What does the evidence say?

Number of included studies/reviews (number of participants)

One systematic review (SR) (Watanabe et al. 2007) and one randomised controlled trial (RCT) (Power et al. 1990) met the inclusion criteria for this BEST summary.

Main findings

The systematic review by Watanabe et al. (2007) aimed to compare psychotherapy plus benzodiazepines with either treatment alone for panic disorder with or without agoraphobia. Two studies with 243 participants (Marks 1993; Wardle 1994) met their inclusion criteria, and both included patients with panic disorder with agoraphobia. To address the inclusion criteria for this BEST summary, we have only reported results for combined treatment vs. psychotherapy alone. The authors found no significant differences between these two groups for response (the primary outcome) at any time period (i.e. at 2 months, immediately after end of drug, or at 6 to 12 months after treatment termination). Combination therapy was also not shown to be superior over psychotherapy alone at 2 to 4 months for the following secondary outcomes: global severity, phobic avoidance, general anxiety, or depression. In addition, there was also no significant difference between groups for global severity immediately after end of drug taper, or 6 to 12 months after treatment (data were not available for the other outcomes at these time periods). Combination therapy was, however superior over psychotherapy alone for panic frequency and social functioning at 2 to 4 months. Based on trends in the evidence, the authors suggested that combined therapy may be “superior to behaviour therapy alone during the acute phase, but this possible superiority may not persist and perhaps invert during the follow-up 6–12 months after treatment termination.” We note, however, that the differences were not statistically significant, so these trends need to be confirmed with further research.

A trial by Power et al. (1990) randomised 113 people with generalised anxiety disorder into one of five treatment arms: cognitive behaviour therapy (CBT) alone, diazepam alone, placebo, diazepam plus CBT, and placebo plus CBT. For the purposes of this BEST summary, we have reported the results for the diazepam plus CBT group vs. CBT alone, and CBT vs. CBT plus placebo groups. The authors reported no significant differences between these three groups at any time period (i.e. after 6 weeks double-blind treatment, at 70 days [one week after treatment had ceased], or at 6 months-follow-up) for anxiety (measured using the measured using the HAM-A), distress (using the Kellner and Sheffield Symptom Rating Test (SRT)), or using the General Health Questionnaire (GHQ)

(including somatic symptoms; anxiety and insomnia; dysfunction; severe depression). All three groups demonstrated significant within group improvements over time.

Authors conclusions

Watanabe et al. (2007) concluded that they found little high quality evidence for or against psychotherapy plus benzodiazepine therapy for panic disorder.

Power et al. (1990) did not make definite conclusions, but noted in their discussion that diazepam plus CBT demonstrated early treatment gains, and that this combined treatment may be most appropriate for people with moderate to severe generalised anxiety disorder.

Reliability of conclusions/Strength of evidence

The SR by Watanabe et al. (2007) was well conducted, and the authors' cautious conclusions are likely to be reliable. The authors appropriately noted a number of limitations of the two studies included in their review, including limited generalisability (e.g. both studies were conducted at psychiatric hospitals).

Information on randomisation methods and allocation concealment were not reported in the RCT by Power et al. (1990), and given that the randomised groups had small sample sizes, the results are unlikely to be reliable.

What do guidelines say?

Neither National Institute for Health and Care Excellence (NICE) nor Scottish Intercollegiate Guidelines Network (SIGN) guidelines comment on the impact of concurrent Benzodiazepine use on the effectiveness of psychological therapies.

Date question received: 19/05/2015

Date searches conducted: 22/05/2015

Date answer completed: 29/05/2015

References

Systematic reviews

Watanabe, N., Churchill, R., & Furukawa, T. A. (2007). Combination of psychotherapy and benzodiazepines versus either therapy alone for panic disorder: a systematic review. *BMC Psychiatry*, 7(1), 18.

Randomised Controlled Trials

Power, K. G., Simpson, R. J., Swanson, V., Wallace, L. A., Feistner, A. T. C., & Sharp, D. (1990). A controlled comparison of cognitive-behaviour therapy, diazepam, and placebo, alone and in combination, for the treatment of generalised anxiety disorder. *Journal of Anxiety Disorders*, 4(4), 267-292.

Results

Systematic reviews

Author (year)	Search date	Inclusion criteria	Number of included studies	Summary of results	Risk of bias
Watanabe et al. (2007)	05/2015	<p><i>Participants:</i> (i) Adults diagnosed with panic disorder and agoraphobia according to Diagnostic & Statistical Manual of Mental Disorders v.III (DSM-III) or International Classification of Disease v.9 (ICD-9) (Study One); (ii) Adults diagnosed with agoraphobia by DSM-III-R (Study Two).</p> <p><i>Intervention:</i> (i) Exposure therapy plus Alprazolam (benzodiazepine) over 16 weeks, with Alprazolam tapered to zero in weeks 9-16 (mean dose: 5.8mg/day) (Study One). (ii) Diazepam (mean dose: 5mg/day) for 16 weeks (tapered to zero in weeks 13-16), plus exposure therapy (8 weeks duration, from weeks 4-12) (Study Two).</p> <p><i>Comparator:</i> (i). Exposure therapy plus pill placebo; Alprazolam alone plus psychological placebo</p>	2 RCTs with 243 participants	<p>Psychotherapy plus benzodiazepine versus psychotherapy</p> <p>Acute phase treatment (2-4 months): There was no significant improvement in response for the combined treatment group at 2 months: RR 1.25 (95% CI: 0.78 to 2.03; P = 0.35, 2 studies, n=166). No heterogeneity was observed between the studies.</p> <p>For secondary outcomes, combination therapy was not shown to have significant improvement over psychotherapy alone for global severity (SMD 0.15 [95% CI: -0.21, 0.50], 2 studies, n=122), phobic avoidance (SMD 0.09 [95% CI: -0.27, 0.45], 2 studies, n=122), general anxiety (SMD 0.08 [95% CI: -0.43, 0.59], 1 study, n=60), or depression (SMD 0.17 [95% CI: -0.23, 0.58], 2 studies, n=120).</p> <p>Combination therapy was superior for panic frequency (SMD 0.38 [95% CI: 0.02 to 0.72],</p>	Low

		<p>(relaxation); Psychological placebo plus pill placebo- over 16 weeks (Study One). (ii). Exposure therapy plus pill placebo (Study Two).</p> <p><i>Outcome:</i> Both studies: Global severity of panic disorder; no. of panic attacks; agoraphobia (measured by Mobility Index- Mobility Alone); General anxiety; Depression. Study Two only: Social Functioning.</p> <p><i>Study design:</i> Randomised controlled trials.</p>		<p>P = 0.04, 2 studies, n=124) and social functioning (SMD 0.51 [95% CI: 0.01 to 1.01], P = 0.05, 1 study, n=64). Both combination therapy and psychotherapy alone groups had similar dropout rates (RR 0.81 [95% CI: 0.47 to 1.38], P = 0.44, 2 studies, n=166).</p> <p>Immediately after end of drug taper: There was no significant improvement in response for the combined treatment group (RR 0.78 [95% CI: 0.45 to 1.35], P = 0.37, 2 studies, n=166). No heterogeneity was observed between the studies. There was also no significant difference between groups for global severity (SMD - 0.31 [95% CI -0.71 to 0.09], P = 0.12, 2 studies, n=99) (data were not available for other outcomes).</p> <p>6–12 months after treatment termination: There was no significant improvement in response for the combined treatment group (RR 0.62 [95% CI: 0.36 to 1.07], P = 0.08, 2 studies, n=166). No heterogeneity was observed between the studies. There was also no significant difference between groups for global severity (SMD -0.19 [95% CI: -0.59 to 0.22, P = 0.37), 2 studies, n=95)</p>	
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				(data were not available for other outcomes). This review also reported results for psychotherapy plus benzodiazepine versus benzodiazepine, but this was not extracted as it was not relevant to this BEST question.	
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RCTs






Author (year)	Inclusion criteria	Number of participants	Summary of results	Risk of bias
Power et al. (1990)	<p><i>Participants:</i> Patients aged 18-65 with (i) a primary diagnosis of Generalised Anxiety Disorder, according to DSM-III and Research Diagnostic Criteria; (ii) a minimum score of 15 on the Hamilton Rating Scale for Anxiety (HAM-A); (iii) symptoms that had lasted at least one month; (iv) no ongoing Benzodiazepine use; (v) no current psychotropic drug use.</p> <p><i>Intervention:</i> Cognitive Behavioural Therapy (CBT) (for a maximum of 7 weeks within an overall 10 week period), plus Diazepam (5mg p/day in weeks 1-6, tapered to zero in weeks 7-10).</p> <p><i>Comparator:</i> Over 10 weeks: CBT alone (7 weeks maximum); Diazepam</p>	N=113 randomised (101 included in the analysis)	<p>Anxiety After the 6 weeks double-blind period, mean anxiety scores (measured using the HAM-A) were 5.1 (SD 3.3) in the diazepam plus CBT group, 7.6 (SD 5.0) in the CBT alone group, and 7.8 (SD 5.5) in the placebo plus CBT group, but no significant differences between groups were reported. After 70 days (one week after ceasing all medication), mean anxiety scores were 4.0 (SD 4.2) in the diazepam plus CBT group, 5.2 (SD 4.8) in the CBT alone group, and 7.0 (SD 5.4) in the placebo plus CBT group, but no significant differences between groups were reported at any time period. Within group analysis demonstrated that all three treatments resulted in significant reductions in scores.</p>	High (due to small sample sizes in each group)

	<p>alone; Pill placebo alone; CBT plus pill placebo.</p> <p><i>Outcome:</i></p> <p>(i) Anxiety, measured by the HAM-A; (ii) Changes in symptoms of distress, measured by the Kellner and Sheffield Symptom Rating Test (SRT); (iii) General health, measured by the General Health Questionnaire (GHQ); (iv) Adverse reactions to medication.</p>		<p>Distress</p> <p>After the 6 weeks double-blind period, mean scores to measure distress (using the Kellner and Sheffield Symptom Rating Test (SRT)) were 13.6 (SD 10.5) in the diazepam plus CBT group, 18.0 (SD 13.9) in the CBT alone group, and 19.6 (SD 14.9) in the placebo plus CBT group, but no significant differences between groups were reported. After 70 days (one week after ceasing all medication), mean distress scores were 9.9 (SD 10.4) in the diazepam plus CBT group, 12.5 (SD 13.9) in the CBT alone group, and 16.8 (SD 11.7) in the placebo plus CBT group, but no significant differences between groups were reported at any time period. Within group analysis demonstrated that all three treatments resulted in significant reductions in scores.</p> <p>General Health Questionnaire (GHQ)</p> <p>Total scores and individual scores (somatic symptoms; anxiety and insomnia; dysfunction; severe depression) at 70 days were not significantly different between the diazepam plus CBT, CBT alone, or CBT plus placebo groups (no data were reported separately for week 42).</p>	
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





			<p>The authors stated that “on all measures the DZ plus CBT group consistently [had] the largest percentage of patients showing ‘clinically significant change’. The CBT groups [showed] a similarly consistent pattern of improvement, although the magnitude of the effect [was] less pronounced.” The authors also reported that at 6 month follow-up, the DZ plus CBT, and CBT group had maintained initial treatment gains (although we note that sample sizes are small).</p> <p>This study also reported results for diazepam alone, and placebo alone, but data for these groups were not extracted as they were not relevant to this BEST question.</p>	
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Risk of bias:

Systematic reviews

Author (year)	Risk of Bias				
	Inclusion criteria	Searches	Review process	Quality assessment	Synthesis
Watanabe et al. (2007)					

Randomised controlled trials

Study	RISK OF BIAS					
	Random allocation	Allocation concealment	Blinding of participants and personnel	Blinding of outcome assessment	Incomplete outcome data	Selective Reporting
Power et al. (1990)						

 Low risk

 High risk

 Unclear risk

Search details

Source	Search Strategy	Number of hits	Relevant evidence identified
<i>Guidelines</i>			
NICE	Benzodiazepine Psychotherapy	28	0
	Benzodiazepine Psychological	95	0
<i>Systematic Reviews</i>			
DARE	1 MeSH DESCRIPTOR Cognitive Therapy EXPLODE ALL TREES 785 Delete 2 MeSH DESCRIPTOR Psychotherapy EXPLODE ALL TREES 2087 Delete 3 MeSH DESCRIPTOR Psychotherapy, Brief EXPLODE ALL TREES 64 Delete 4 MeSH DESCRIPTOR Psychotherapy, Group EXPLODE ALL TREES 211 Delete 5 MeSH DESCRIPTOR Psychotherapy, Multiple EXPLODE ALL TREES 0 Delete 6 MeSH DESCRIPTOR Psychotherapy, Psychodynamic EXPLODE ALL TREES 1 Delete 7 MeSH DESCRIPTOR Psychotherapy, Rational-Emotive EXPLODE ALL TREES 2 Delete 8 MeSH DESCRIPTOR Art Therapy EXPLODE ALL TREES 16 Delete 9 MeSH DESCRIPTOR Behavior Therapy EXPLODE ALL TREES 1314 Delete 10 MeSH DESCRIPTOR Couples Therapy EXPLODE ALL TREES 11 Delete 11 MeSH DESCRIPTOR Gestalt Therapy EXPLODE ALL TREES 1 Delete 12 MeSH DESCRIPTOR Imagery (Psychotherapy) EXPLODE ALL TREES 19 Delete 13 MeSH DESCRIPTOR Mind-Body Therapies EXPLODE ALL TREES 496 Delete 14 MeSH DESCRIPTOR Narrative Therapy EXPLODE ALL TREES 1 Delete 15 MeSH DESCRIPTOR Nondirective Therapy EXPLODE ALL TREES 3 Delete 16 MeSH DESCRIPTOR Psychodrama EXPLODE ALL TREES 4 Delete 17 MeSH DESCRIPTOR Mindfulness EXPLODE ALL TREES 13 Delete 18 MeSH DESCRIPTOR Acceptance and Commitment Therapy EXPLODE ALL TREES 2 Delete 19 MeSH DESCRIPTOR Family Therapy EXPLODE ALL TREES 82 Delete 20 (CBT or psychotherap* or psychodynamic or psychoanaly* or Gestalt or couneslling or mindful* or CAT or	42	1

	<p>ACT or Jungian or EMDR) IN DARE 1237 Delete</p> <p>21 ((Integrative or cognitive or behavior?r* or Compassion* or Narrative or systemic or family or acceptance or psychodrama or cognitive analytic or Person-cent?red or solution-focused or drama or music or interpersonal) adj2 therapy) IN DARE 1496 Delete</p> <p>22 MeSH DESCRIPTOR Benzodiazepines EXPLODE ALL TREES 290 Delete</p> <p>23 (Alprazolam or Bentazepam or Bretazenil or Bromazepam or Brotizolam or Camazepam or Chlordiazepoxide or Cinolazepam or Clonazepam or Clotiazepam or Delorazepam or Deschloroetizolam or Diazepam or Diclazepam or Estazolam or Ethyl carfluzepate or Etizolam or Ethyl loflazepate or Flubromazepam or Flunitrazepam or Flurazepam or Halazepam or Ketazolam or Loprazolam or Lorazepam or Lormetazepam or Medazepam or Midazolam or Nimetazepam or Nitrazepam or Nordiazepam or Oxazepam or Phenazepam or Pinazepam or Prazepam or Premazepam or Pyrazolam or Quazepam or Temazepam or Tetrazepam or Triazolam) IN DARE 242 Delete</p> <p>24 #1 OR #2 OR #3 OR #4 OR #5 OR #6 OR #7 OR #8 OR #9 OR #10 OR #11 OR #12 OR #13 OR #14 OR #15 OR #16 OR #17 OR #18 OR #19 OR #20 OR #21 3056 Delete</p> <p>25 #22 OR #23 470 Delete</p> <p>26 #24 AND #25 42 Delete</p>		
<i>Primary Studies</i>			
MEDLINE	<ol style="list-style-type: none"> 1. Medline; exp "IMAGERY (PSYCHOTHERAPY)"/ OR exp PSYCHOTHERAPY/ OR exp PSYCHOTHERAPY, BRIEF/ OR exp PSYCHOTHERAPY, GROUP/ OR exp PSYCHOTHERAPY, MULTIPLE/ OR exp PSYCHOTHERAPY, PSYCHODYNAMIC/ OR exp PSYCHOTHERAPY, RATIONAL-EMOTIVE/; 161662 results. 2. Medline; exp COGNITIVE THERAPY/; 17054 results. 3. Medline; exp BENZODIAZEPINES/; 58867 results. 4. Medline; exp RANDOMIZED CONTROLLED TRIALS AS TOPIC/; 97095 results. 5. Medline; exp RANDOM ALLOCATION/; 82519 results. 6. Medline; exp DOUBLE-BLIND METHOD/; 128166 results. 7. Medline; exp SINGLE-BLIND METHOD/; 20126 results. 8. Medline; exp CLINICAL TRIAL/ OR exp CLINICAL TRIAL, PHASE I/ OR exp CLINICAL TRIAL, PHASE II/ OR exp CLINICAL TRIAL, PHASE III/ OR exp CLINICAL TRIAL, PHASE IV/ OR exp CLINICAL TRIALS AS TOPIC/; 285400 results. 	218	1

	<p>9. Medline; 4 OR 5 OR 6 OR 7 OR 8; 472373 results.</p> <p>10. Medline; (clinical ADJ trial*).ti,ab; 227512 results.</p> <p>11. Medline; (((singl* OR doubl* OR treb* OR tripl*) ADJ (blind* OR mask*))).ti,ab; 133865 results.</p> <p>12. Medline; exp PLACEBOS/; 32558 results.</p> <p>13. Medline; (randomly AND allocated).ti,ab; 21206 results.</p> <p>14. Medline; ((allocated adj2 random*).ti,ab; 21296 results.</p> <p>15. Medline; 10 OR 11 OR 12 OR 13 OR 14; 378465 results.</p> <p>16. Medline; 9 OR 15; 669081 results.</p> <p>17. Medline; (case-control OR epidemiolog* OR observational OR cohort OR longitudinal).ti,ab; 788424 results.</p> <p>18. Medline; 16 OR 17; 1421426 results.</p> <p>19. Medline; 1 AND 3 AND 18; 218 results.</p>		
CINAHL	<p>1. CINAHL; exp PSYCHOTHERAPY/ OR exp PSYCHOTHERAPY,BRIEF/ OR exp PSYCHOTHERAPY,PSYCHODYNAMIC/ OR exp COGNITIVE THERAPY/ OR exp PSYCHOTHERAPY,GROUP/; 91178 results.</p> <p>2. CINAHL; (CBT OR psychotherap* OR psychodynamic OR psychoanaly* OR Gestalt OR couneslling OR mindful* OR CAT OR ACT OR Jungian OR EMDR).ti,ab; 29919 results.</p> <p>3. CINAHL; ((integrative adj3 therapy) OR (cognitive adj3 therapy) OR (compassion* adj3 therapy) OR (narrative adj3 therapy) OR (systemic adj3 therapy) OR (family adj3 therapy) OR (acceptance adj3 therapy) OR (analytic* adj3 therapy) OR (person-cent?red adj3 therapy) OR (solution-focused adj3 therapy) OR (interpersonal adj3 therapy) OR (cognitive?analytic*) OR (cognitive adj2 analytic*) OR (mindful* adj3 therapy) OR (mindful* adj2 based)).ti,ab; 3590 results.</p> <p>4. CINAHL; 1 OR 2 OR 3; 116678 results.</p> <p>5. CINAHL; exp ANTIANXIETY AGENTS,BENZODIAZEPINE/; 0 results.</p> <p>6. CINAHL; ((Alprazolam OR Bentazepam OR Bretazenil OR Bromazepam OR Brotizolam OR Camazepam OR Chlordiazepoxide OR Cinolazepam OR Clonazepam OR Clotiazepam OR Delorazepam OR Deschloroetizolam OR Diazepam OR Diclazepam OR Estazolam OR Ethyl carfluzepate OR Etizolam OR Ethyl loflazepate OR Flubromazepam OR Flunitrazepam OR Flurazepam OR Halazepam OR Ketazolam OR Loprazolam OR Lorazepam OR Lormetazepam OR Medazepam OR Midazolam OR Nimetazepam OR Nitrazepam OR Nordiazepam OR Oxazepam OR Phenazepam OR Pinazepam OR Prazepam OR Premazepam OR Pyrazolam OR Quazepam OR Temazepam OR Tetrazepam OR Triazolam)).ti,ab; 2124 results.</p>	61	1

	7. CINAHL; 4 AND 6; 61 results.		
PsycINFO	<p>2. PsycInfo; exp COGNITIVE BEHAVIOR THERAPY/ OR exp PSYCHOTHERAPY/ OR exp COGNITIVE THERAPY/ OR exp BEHAVIOR MODIFICATION/ OR exp COGNITIVE RESTRUCTURING/ OR exp RATIONAL EMOTIVE BEHAVIOR THERAPY/ OR exp PSYCHOTHERAPEUTIC TECHNIQUES/ OR exp COUPLES THERAPY/ OR exp COGNITIVE TECHNIQUES/ OR exp ANXIETY MANAGEMENT/ OR exp SELF MANAGEMENT/ OR exp SELF INSTRUCTIONAL TRAINING/; 105431 results.</p> <p>3. PsycInfo; ((integrative adj3 therapy) OR (cognitive adj3 therapy) OR (compassion* adj3 therapy) OR (narrative adj3 therapy) OR (systemic adj3 therapy) OR (family adj3 therapy) OR (acceptance adj3 therapy) OR (analytic* adj3 therapy) OR (person-cent?red adj3 therapy) OR (solution-focused adj3 therapy) OR (interpersonal adj3 therapy) OR (cognitive?analytic*) OR (cognitive adj2 analytic*) OR (mindful* adj3 therapy) OR (mindful* adj2 based)).ti,ab; 23691 results.</p> <p>4. PsycInfo; (CBT OR psychotherap* OR psychodynamic OR psychoanaly* OR Gestalt OR counselling OR Jungian OR EMDR OR mindfulness-based).ti,ab; 182955 results.</p> <p>5. PsycInfo; 2 OR 3 OR 4; 247395 results.</p> <p>6. PsycInfo; exp BENZODIAZEPINES/; 4560 results.</p> <p>7. PsycInfo; (Alprazolam OR Diazepam OR Clonazepam OR Lorazepam OR Temazepam).ti,ab; 7437 results.</p> <p>8. PsycInfo; 6 OR 7; 10768 results.</p> <p>9. PsycInfo; 5 AND 8; 316 results.</p>	316	1

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