

14. Appendices: 1-4

Interventions for panic disorder

Appendix 1:

Pharmacological compared with psychological
compared with combination interventions for
panic disorder

Meta analyses, systematic reviews and other reviews

Meta analysis/systematic review extraction table

Author (s)	Research question	Review type Databases used Time period covered Data analysis	Study design Interventions Follow-up period	Numbers randomised Randomisation method Numbers incl in results analysis (Confirm ITT analysis or % included in results)	Total sample number Age (mean/SD/range) Male/female Ethnicity	Outcomes
<p>Van Balkom et al 'A meta-analysis of the treatment of panic disorder with or without agoraphobia: a comparison of psychopharmacological, cognitive-behavioural, and combination treatments'</p> <p>in <i>The Journal of Nervous and Mental Disease</i> 1997 pp510-516</p>	<p>To compare the short term efficacy of benzodiazepines, antidepressants, psychological panic management, exposure in vivo and combination treatments in panic disorder with or without agoraphobia.</p>	<p>Review type: meta-analysis</p> <p>Databases used: Excerpta medica 1964-1995 PsycINFO 1964-1995 Index medicus 1964-1995</p> <p>Data analysis: Calculation of effect sizes using Cohen's <i>d</i> calculated within treatments as most studies did not include a control condition</p> <p>ANOVA assumptions of normality and homogeneity of variance of effect sizes were not met. Kruskal-Wallis one-way ANOVA by ranks on differences between treatment conditions on demographic and psychiatric status variables, total quality score and the magnitude of the effect sizes. Bonferroni correction applied depending on the number of comparisons.</p>	<p>Meta-analysis</p> <p>Interventions: benzodiazepines, antidepressants, psychological panic management, exposure in vivo and combination treatments</p> <p>Follow-up: see Bakker 1998</p> <p>+</p> <p>DURATION OF TREATMENT NOT STATED</p>	<p>Numbers randomised=5,011 Intent to treat conducted in only 8% of studies</p> <p>Randomisation method: Not specified.</p> <p>Data is analysed on the number of completers N=4016</p>	<p>Total sample number (analysed) = 4016</p> <p>Age (SD), M/F ratio control 35.1 (7.2) .3</p> <p>Age (SD), M/F ratio High potency BDZ 36 (2.3) .7</p> <p>Age (SD), M/F ratio antidepressants 32.9 (6.5) .4</p> <p>Age (SD), M/F ratio psychological panic management 35.9(3.0) .4</p> <p>Age (SD), M/F ratio exposure in vivo 37.4 (4.0), .2</p> <p>Age (SD), M/F ratio pill placebo + exposure in vivo 36.3 (3.3), .2</p> <p>Age (SD), M/F ratio antidepressants + exposure in vivo 35.7 (3.2), .2</p> <p>Age (SD), M/F ratio Psychological panic management + exposure 36.4 (2.9), .2</p>	<p>Effect sizes and standard deviations for</p> <p>Panic</p> <p>Agoraphobia</p> <p>Depression</p> <p>Anxiety on patients were administered:</p> <p>High-potency benzodiazepines, antidepressants, psychological panic management, exposures in vivo, pill-placebo +exposure in vivo, antidepressants+exposure in vivo, antidepressants +exposure in vivo or psychological panic management</p>
<p>Results: treatment, comparator data, dropouts (numbers/percentage and reasons), treatment emergent adverse events (whether spontaneous report or questioned by researcher/treating clinician), investigator's conclusions and reviewers conclusions if different from investigators</p>						

Note on diagnostic criteria of included studies: DSM-III-R used in 61 or 27% of treatment conditions, DSM-III used in 95 or 43% of treatment conditions. In the remaining conditions, i.e. 66 or 33% of treatment conditions, patients were diagnosed as agoraphobic. The use of DSM-III-R vs DSM-III significantly influenced the magnitude of the effect sizes for agoraphobia: chi square=7.3, df=2, N=198, p=.03. Diagnostic criteria used did not significantly influence effect sizes for panic: chi square=5.4, df=2, N=135, p=.07

a= that effect sizes (denoted by *d*) are different from the effect-size of the control-condition at $p < .007$, one tailed; b-f=treatment conditions are different at $p < .002$ two-tailed

Control

Panic <i>d</i> .53	Agoraphobia <i>d</i> .32	Depression <i>d</i> .32	Anxiety <i>d</i> .51
SD .47	.55	.36	.54
N 23	25	15	21

High potency BDZ

Panic <i>d</i> 1.14a	Agoraphobia <i>d</i> 1.00 ab	Depression <i>d</i> .69	Anxiety <i>d</i> 1.18a
SD .58	.59	.36	.54
N 25	17	15	21

Antidepressants

Panic <i>d</i> 1.02a	Agoraphobia <i>d</i> 1.02ac	Depression <i>d</i> 1.03a	Anxiety <i>d</i> 1.40a
SD .67	.44	.62	.76
N 18	15	14	19

Psychological panic management

Panic <i>d</i> 1.25a	Agoraphobia <i>d</i> .91ad	Depression <i>d</i> 1.00a	Anxiety <i>d</i> 1.30a
SD .62	.54	.75	.81
N 23	26	23	18

Exposure in vivo

Panic <i>d</i> .79	Agoraphobia <i>d</i> 1.38	Depression <i>d</i> .64b	Anxiety <i>d</i> 1.02ab
SD .41	.84	.56	.70
N 12	52	27	32

Pill placebo + exposure in vivo

Panic <i>d</i> .85	Agoraphobia <i>d</i> 1.60a	Depression <i>d</i> .76	Anxiety <i>d</i> .95
SD .69	.94	.23	1.27
N 6	11	5	8

Antidepressants + exposure in vivo

Panic <i>d</i> 1.79	Agoraphobia <i>d</i> 2.47 ab-f	Depression <i>d</i> 1.77abc	Anxiety <i>d</i> 2.00abc
SD .73	.82	.59	.47
N 5	8	7	6

Psychological panic management + exposure

Panic <i>d</i> .96	Agoraphobia <i>d</i> 1.22af	Depression <i>d</i> .69c	Anxiety <i>d</i> .89ac
SD .71	.60	.45	.54
N 13	28	17	19

Antidepressants, psychological panic management and antidepressants combined with exposure in vivo were significantly superior to control condition on the four clinical variables. It is notable that psychological panic management alone is superior to this treatment in combination with exposure in vivo. The authors discovered that, on closer inspection, in the combination studies, at least half of the protocol time is spent on panic management and half on exposure in vivo (unlike psy. Panic management alone where all the time is spent on panic management). There were no significant differences were found between treatments on panic attacks. Mann-Whitney tests revealed that antidepressants combined with exposure in vivo were significantly superior to exposure in vivo alone and psychological panic management combined with exposure on depression. Multiple regression analysis to compare the 7 active treatments anxiety revealed no large differences between the treatments for panic. When confounders were controlled it was found that high-potency BDZs and the combination of antidepressants with exposure in vivo accounted for 7% of variance, indicating the relative superiority of the combination treatment above the other treatments and an inferior effectiveness of the BDZs

Meta analysis/systematic review extraction table

Author (s)	Research question	Review type Databases used Time period covered Data analysis	Study design Interventions Follow-up period	Numbers randomised Randomisation method Numbers incl in results analysis (Confirm ITT analysis or % included in results)	Total sample number Age (mean/SD/range) Male/female Ethnicity	Outcomes
<p>Gould et al A meta-analysis of treatment outcome for panic disorder</p> <p>In <i>Clinical Psychology Review</i>_Vol. 15 1995</p>	<p>Comparison of efficacy of cognitive behavioural vs pharmacological vs combined treatments for panic disorder.</p>	<p>Meta-analysis Databases used: CD ROM PSYCHLIT 1974-1994; MEDLINE CD ROM: 1974-1994 Secondary references from reference sections of treatment studies located in above two databases; Articles in press if known prior to March 1994.</p> <p>43 studies included with 76 treatment comparisons</p>	<p>RCTs of studies for patients with PD with or without agoraphobia.</p> <p>Cognitive behavioural (including cognitive interventions alone, cognitive restructuring plus situational exposure, cognitive-restructuring plus interoceptive exposure and other interventions), Pharmacological studies (including antidepressants, benzodiazepines and others) and combined treatments Follow-up period:</p>	<p>Numbers randomised Not stated Randomisation method: Not stated ITT analysis: Not stated</p>	<p>Total sample number: Stated for each paper Age: Not provided Male/Female 24%/76% Ethnicity: Not provided</p>	<p>Mean overall effect sizes across dependent measures. Mean effect sizes for panic frequency Dropout rates Sample size</p>

Results: treatment, comparator data, dropouts (numbers/percentage and reasons), treatment emergent adverse events (whether spontaneous report or questioned by researcher/treating clinician), investigator's conclusions and reviewers conclusions if different from investigators

Caution: dependent (outcome) measures are not stated

Pharmacotherapy interventions (Antidepressants vs Benzodiazepines) (16 studies):

Mean overall effect size of pharmacotherapy: 0.47 $p < 0.0001$ (95% C.I. = 0.38 to 0.54)

9 studies measured Antidepressants vs control. Mean effect size = 0.55, $p < 0.0001$ & Benzodiazepines vs control, 13 studies mean effect size = 0.40 $p < 0.0001$

There was no significant difference between antidepressants and benzodiazepines, $p = .09$. Proportion of dropouts were 25.4% Ads, 13.1% BDZs & 32.5% pill placebo

Cognitive Behavioural Interventions (19 studies, 832 patients):

Mean overall effect size = 0.68 $p < 0.0001$ (C.I. = 0.58 to 0.78). Mean effect size for panic-free rate was 74.3% compared with 27.1% for controls.

Dropout rate for those in the treatment arms was 5.6% and 7.2% for the control groups.

Note, where situational exposure was used as a control, these studies were eliminated and effect sizes recalculated. Mean overall effect size was 0.68 and panic frequency effect size was 0.55 and panic-free rate was 70%.

Authors note that it is difficult to make direct comparisons between the different kinds of cognitive behavioural intervention due to studies using different comparison groups (e.g. wait-list and situational exposure). In studies where interoceptive exposure was combined with cognitive restructuring (7 studies) compared to wait-list or supportive therapy, mean effect sizes were 0.88 and panic frequency effect size was 0.66.

Pharmacotherapy vs Cognitive Behavioural Therapy:

In comparison, CBT fares better in both overall effect sizes (0.68) compared to pharmacotherapy treatments (0.47). This result is statistically significant ($t(58)=1.99$; $p=.05$). CBT interventions yielded greater panic-free rates of 70% compared to 57% for Pharmacotherapies. However, differences in panic frequency effect sizes of 0.55 for CBT and 0.53 for Pharmacotherapies were similar and not statistically significant. When compared to more recent CBT approaches that incorporated interoceptive exposure and cognitive restructuring, CBT yielded higher effect sizes again of 0.88 compared to 0.47 for pharmacotherapy treatments. This difference was statistically significant ($t(34)=4.65$; $p=.0001$). Dropout rates were higher in the pharmacotherapy group than those in the CBT groups (20% vs 6%).

The authors point out that in these comparisons, account should be taken of control groups used: pill-placebo control groups have higher panic-free rates than wait-list controls (35% vs 28%). Pharmacotherapy trials used pill-placebo control rather than a wait-list condition (88% vs 0%). CBT is more likely to use a wait-list condition compared to pill-placebo (44% vs 6%). In other words, it is harder to do well against pill-placebo than it is against wait-list control.

Combined Pharmacologic and Cognitive-Behavioural Treatments:

Relatively few studies combined pharmacologic and psychological interventions. Of the 8 that did so, 6 looked at exposures with imipramine. The mean effect size was 0.56 (95% C.I. = 0.47 to 0.65). This result was not statistically different when imipramine was looked at alone (ES=0.55). The authors report that these studies did not report panic-free rates. The mean effect size for panic frequency was -0.08(!). They say that this suggests that the combined approach was 'relatively not more effective in reducing number of panic attacks'. Drop-out rates for imipramine combined with CBT were the same as imipramine alone (i.e. 22%). One of the studies reported combined the black-listed alprazolam and is not reported here.

Within each of the above study division, a certain number of each examined black-listed treatments (table of studies to follow).

Investigator's conclusion:

For patients with a primary diagnosis of panic disorder, the available evidence confers a number of advantages for cognitive-behavioural treatment and encourages increased clinical utilization of these interventions. Notwithstanding the issue of different control conditions (i.e. those studies utilizing pill-placebo being more difficult to 'beat' than those using wait-list control), the authors maintain this conclusion is upheld.

Meta analysis/systematic review extraction table

Author (s)	Research question	Review type Databases used Time period covered Data analysis	Study design Interventions Follow-up period	Numbers randomised Randomisation method Numbers incl in results analysis (Confirm ITT analysis or % included in results)	Total sample number Age (mean/SD/range) Male/female Ethnicity	Outcomes
<p>Bakker et al (1998) 'Follow-up on the treatment of panic disorder with or without agoraphobia: a quantitative review' in <i>The Journal of Nervous and Mental Disease</i> vol 186(7) pp414-419</p>	<p>Follow-up of Gould et al's meta-analysis to find out whether antidepressants with exposure in vivo remain superior or whether there is a shift in the follow-up period toward preferable outcome with cognitive-behavioural techniques</p>	<p>Review type: meta-analysis: 106 studies included in the VanBalkom meta-analysis were reviewed for follow-up data (therefore the time period was from the date of the included study within the 1964 to 1995 search). Also searched: psychInfo, Indes Medicus, and Excerpta Medica (screened for follow-up data on short-term studies).</p> <p>Data analysis:</p>	<p>Study design: not specified</p> <p>Interventions: benzodiazepines, antidepressants, psychological panic management, exposure in vivo and combination treatments</p> <p>Follow-up period: MEAN DURATION=62 (+/-) 89 weeks. Range: 4 weeks (7 studies) to 8 years (4 studies)</p>	<p>Numbers randomised: 2173 participated in the 68 included studies and 1862 were included in the posttest analysis</p> <p>No ITT analysis</p>	<p>Total sample number = 2173</p> <p>Age = cf van Balkom et al 1997</p> <p>Male/female ratio – not provided</p> <p>Ethnicity not provided</p>	<p>Effect Sizes using Cohen's <i>d</i> for measures of panic and agoraphobia</p>

Results: treatment, comparator data, dropouts (numbers/percentage and reasons), treatment emergent adverse events (whether spontaneous report or questioned by researcher/treating clinician), investigator's conclusions and reviewers conclusions if different from investigators

Effect sizes at post-test were strong predictors of effect sizes at follow-up. Spearman correlation coefficient for posttest with follow-up text for panic: $r=.82$, $N=49$, $p<.0001$; agoraphobia: $r=.69$, $N=100$, $p<.001$

Overall mean change for panic during the follow-up period: range 1.11 +/-0.70 at posttest to 1.28 +/-0.61 at follow-up test (Wilcoxon test, panic: $Z=2.30$, $N=49$, $p=.02$)

Overall mean change for agoraphobia 1.36 +/-1.10 at posttest and 1.41 +/-0.82 at follow up; Wilcoxon test, agoraphobia: $Z=1.39$, $N=100$, $p=.17$

No relationship was found between the number of dropout per treatment and the magnitude of the effect size:

Spearman correlation for panic: $r=.15$, $N=44$, $p=.34$; agoraphobia: $r=.08$, $N=96$, $p=.47$

Duration of follow-up did not effect the magnitude of the effect sizes:

Spearman correlation coefficient panic: $r=.01$, $N=46$, $p=.95$; agoraphobia: $r=.15$, $N=98$, $p=.15$

The authors note a striking difference between the numbers in follow-up pharmacotherapy studies and the numbers in follow-up psychological studies

Control

In 17 of the treatment conditions (16%) no treatment was given between posttest and follow-up. These included one of the benzodiazepines studies, 6 of the psychological panic management studies, 6 of the exposure in vivo and 4 of the psychological panic management combined with exposure in vivo, i.e. 89 conditions or 84% at follow-up were naturalistic in character and were not controlled for the treatments received.

Not all studies provided complete information at follow-up and this is indicated by the scale score, "information about follow-up"

Comparison of effect sizes between panic and agoraphobia over all conditions (using Kruskal-Wallis tests) revealed that distribution of panic measures did not differ significantly at posttest and follow-up:

Pre/posttest: $\chi^2=5.23$, $df=5$, $N=54$, $p=.038$; pre/follow-up test: $\chi^2=6.26$, $df=5$, $N=49$, $p=0.28$.

Significant differences were found for agoraphobia:

Pre/posttest $\chi^2=11.40$, $df=5$, $N=103$, $p=0.04$; pre/follow-up test: $\chi^2=17.40$, $df=5$, $N=100$, $p=0.004$

Conclusions: A combination of antidepressants and exposure in vivo is superior to psychological panic management, exposure in vivo and psychological panic management with exposure.

Stated shortcomings of this meta-analysis: Pharma studies had only a few patients at follow-up, (15%) and it is not stated whether they continued to receive medication in the follow-up period.

Psychological studies' conclusions can only be tentative due to the naturalistic nature of the studies and the probability of other treatment being received during the follow-up period.

Psychological Panic Management included all cognitive-behavioural methods to overcome panic attacks and differences in effect sizes could not be demonstrated between them. The authors suggest this being due to the lack of statistical power in the comparison.

In comparing this meta-analysis with van Balkom et al (1997), the authors conclude that present findings concur with this earlier meta-analysis. However, both meta-analysis contrast with that of Gould's in which it is suggested that cognitive-behavioural strategies resulted in the most successful treatment gains and resulted in maintenance of treatment gains.. However, Gould's 1995 met-analysis examined 14 as opposed to 106 treatment conditions and the Gould's follow-up period was considerably shorter (6 months or more).

FOLLOW-UP ON THE TREATMENT OF PANIC DISORDER

TABLE 1

Number of Patients, Duration of follow-up, Information about Treatment during follow-up and Mean Effect-Size Cohen's d at Post-test and at follow-up.

<i>No. of patients</i>	<i>BZD</i>	<i>AD</i>	<i>PPM</i>	<i>EXP</i>	<i>AD+EXP</i>	<i>PPM+EXP</i>
Pre-test	462	89	372	646	71	533
Dropout	58 (13%)	21 (24%)	36 (10%)	106 (16%)	19 (27%)	72 (14%)
Post-test	404	68	336	540	52	461
Lost to follow-up	290 (72%)	24 (35%)	30 (9%)	69 (13%)	8 (15%)	94 (20%)
Follow-up	114	44	306	471	44	367
Duration (weeks) of follow-up (SD)	31.4 (34.7)	31.5 (16.8)	86.0 (117.0)	41.8 (50.2)	121.0 (101.5)	75.1 (116.6)
Information about follow-up, range 1-5 (SD) Panic, pre-post						
d	1.12	1.26	1.16	.78	1.34	1.04
SD	.78	.50	.64	.43	.51	.75
N	7	5	18	11	3	10
Panic pre-follow-up						
d	1.11	1.26	1.16	1.09	1.83	1.42
SD	.22	.69	.60	.44	.78	.38
N	6	5	16	10	3	9
Agoraphobia, pre-post						
d	1.04	.99	0.91	1.34	2.45	1.27
SD	.72	.51	.57	.85	.47	.66
N	7	4	24	43	4	21
Agoraphobia pre-follow-up						
d	1.17	.89	1.10 ^a	1.48 ^b	3.60 ^{a,b,c}	1.23 ^c
SD	.58	.29	.57	.72	.74	.53
N	6	3	23	43	4	21

BZD = high potency benzodiazepines; **AD** = antidepressants; **PPM** = psychological panic management; **EXP** = exposure in vivo; **SD** = standard deviation; *N* = number of treatment conditions.

^{a-c} treatment conditions indicated with the same suffix are different ($p < .003$, two-tailed), according to pairwise comparison (Mann-Whitney test).

Meta analysis/systematic review extraction table

Author (s)	Research question	Review type Databases used Time period covered Data analysis	Study design Interventions Follow-up period	Numbers randomised Randomisation method Numbers incl in results analysis (Confirm ITT analysis or % included in results)	Total sample number Age (mean/SD/range) Male/female Ethnicity	Outcomes
<p>Clum et al A meta-analysis of treatments for panic disorder</p> <p>In Journal of consulting an clinical psychology 1993 vol 61 no. 2, 317-326</p>	<p>To determine the relative effectiveness of pharmacological and psychological treatments of Panic Disorder</p>	<p>Systematic review with meta-analysis</p> <p>Databases used: Psychological abstracts 1964 – 1990</p> <p>Search of specific relevant journals including: <i>J of Clin Psychiatry/ Archives of Gen Psychiatry; Br J. of Psychiatry; Psychotherapy Theory, Research, and Practice; J. of Consulting and Clin Psychology; Behavior Therapy; J. of Behavioral Therapy and Exp. Psychiatry; Behavior Res. and therapy; American J. of Psychiatry;</i> <i>Psychopharmacologia; Comprehensive Psychiatry.</i> In addition, 2 other known studies conducted at Virginia Polytechnic Institute were included</p> <p>(only 1 study predates 1979)</p> <p>Data analysis: Average Effect Size across dependent measures for each study and for each target symptom.</p>	<p>Study design: Studies that contained analysis examinable via the meta-analytic method that dealt with PD or agoraphobia with panic attacks. All studies included a control group. It is not stated whether they were RCTs.</p> <p>Interventions: Antidepressants, High-potency benzodiazepines, other drugs, flooding, psychological coping, combination of drug and psychological treatment</p> <p>Follow-up period: in 9 of the 29 included studies – time period not specified</p>	<p>Numbers randomised: Not provided</p> <p>Randomisation method: Not provided</p> <p>Numbers included in results analysis: (of combined therapies where numbers given – i.e. 7 of 8 studies) = 343</p> <p>ITT analysis not stated and not possible to determine as numbers included not given for 2 studies.</p>	<p>Total sample number (numbers given in 27 of the 29 included studies)= or 1586+</p> <p>Age: Not provided</p> <p>Male/Female ratio: not given</p> <p>Ethnicity: Not given</p>	<p>Panic Symptoms Panic Cognition Avoidance General Anxiety Depression Overall adjustment/disability Panic Attacks Other</p> <p>Results presented as effect sizes by dependent variable and by dependent variable compared with placebo.</p>

Results: treatment, comparator data, dropouts (numbers/percentage and reasons), treatment emergent adverse events (whether spontaneous report or questioned by researcher/treating clinician), investigator's conclusions and reviewers conclusions if different from investigators

Mean effect size within treatments by dependent variable												
Variable	Anti-depressant		High-potency BDZs		Other Drugs		Exposure		Psychological Coping		Combination	
	ES	No. of studies	ES	No. of studies	ES	No. of studies	ES	No. of studies	ES	No. of studies	ES	No. of studies
Panic symptoms	.493	2	.338	1	.3497	3	1.088	3	.559	4	.726	4
Panic cognition		2	.481	1			.598	2	.619	4	.095	1
Avoidance	-.298	2	.346	2	.763	4	1.03	5	.357	8	.588	9
General anxiety	.193	2	.227	4	.987	5	1.565	6	.367	9	1.05	10
Depression	-.078	1	0	1	.417	2	-.78	1	.384	6	-.243	5
Overall adjustment /disability	.437	1	.196	2	.877	1	.442	2	.624	4	.649	5
Panic attacks	.041	1	.452	4	.762	2	1.255	1	.443	8	.575	3
Other	.041								-.096	4		

Mean effect size within treatments compared with placebo by dependent variable												
Variable	Anti-depressant		High-potency BDZs		Other Drugs		Flooding		Psychological Coping		Combination	
	ES	No. of studies	ES	No. of studies	ES	No. of studies	ES	No. of studies	ES	No. of studies	ES	No. of studies
Panic symptoms	.329	3	.032	1	.525	2	1.18	3	.774	1	.851	4
Panic cognition			.36	1			.556	2	.76	1		
Avoidance	.835	3	.346	2	.294	2	1.01	3	1.34	2	1.01	5
General anxiety	1.06	5	.101	4	.447	2	1.87	3	1.68	3	1.30	8
Depression	.28	3	0	1							.374	5
Overall adjustment /disability	.657	2	.196	2			.307	1			.868	3
Panic attacks	.784	1	.418	4	.74	1			.532		.793	3

Effect sizes for treatments were influenced by response to the type of control condition.

The mean duration of illness was grouped for all studies and was found to be of slight significance on effect size (p value not given). Mean durations were divided into three groups: 0-5.9 years (3 studies); 6-9.9 years (8 studies) and 10 years of longer (8 studies). The mean effect size for these three subdivisions were 0.36, 0.46 and 0.62 respectively.

Diagnostic group, i.e. whether there sample in the studies included primarily agoraphobic patients or nonagoraphobic and was found to be nonsignificant. It was noted that frequency of panic attacks was assessed in only 23 comparisons within 15 studies.

Dropouts

Proportion receiving pharmacological interventions: 70 of 466 or 15% and for all of their control groups was 168 of 437 or 38%

Proportion from all psychological interventions: 13 of 69 or 19% and for all their control groups was 8 of 34 or 24%

Proportion from combination therapies: 48 of 183 or 26% and for all the control groups, 25 of 157 or 17%

Note: Control groups in the studies in which combined treatments were examined had the lowest percentage of dropouts, whereas control groups in studies of drugs only, had the highest percentage of dropouts.

Investigator's conclusions:

Psychological coping strategies (Effect Size=1.41) and flooding or exposure (ES = 1.36) are the treatments of choice for panic disorder. These are closely followed by combination treatment (ES = 1.09).

Table 1
Summary of Effect Size for Dropouts, Posttreatment Adjustment, and Follow-up Adjustment

Study	Type of control	Type of treatment	n	Effect size		
				Dropout	Posttreatment	Follow-up
Dunner, Ishiki, Avery, Wilson, & Hyde (1986)	DP	Alprazolam Diazepam	43	-.20 -.37	.48 .68	Not provided
Ballenger et al. (1988)	DP	Alprazolam	481	1.15	.118	Not provided
Pecknold, Swinson, Kuch, & Lewis (1988)	DP	Alprazolam	126	1.51	.428	-.13
Lipsedge et al (1973)	DP	MSD + iproniazid MSD + placebo SSD + iproniazid SSD + placebo Iproniazid	60	Not determinable	2.88 1.98 1.17 1.59 2.30	Not provided
Kathol et al. (1980)	DP	Propranolol	26	Not determinable	.239	Not provided
Uhde et al. (1989)	DP	Clonidine	18	-.36	.391	Not provided
Evans, Kennedy, Schneider, & Hoey (1986)	DP	Imipramine Zimeldine (MAOI)	44	.65 .13	.235 .245	Not provided
Mavissakalian & Michelson (1983)	DP	Imipramine + flooding Imipramine Flooding		Not determinable	.5881 .567 .492	Not provided
Johnston, Trayer, & Whitsett (1988)	DP + investigator sup	Clomipramine	70	-.27	.76	Not provided
Sheehan, Ballenger, & Jacobsen (1980)	DP + sup group therapy	Phenelzine + sup Imipramine + sup	52	-.54 -.28	1.22 .80	Not provided
Charney et al. (1986)	DP + weekly psy	Trazodone + psy Alaprazolam + psy Imipramine + psy	74	-.36 -.44 0	.57 .683 .862	Not provided
Klosko, Barlow, Tassinari, & Cerny (1980)	DP WL	Alprazolam Panic control treatment	57	1.39 (DP) 0(WL) .79 (DP) -.6 (WL)	.117 .547 .773 1.23	Not provided
Chambless, Foa, Groves, & Goldstein (1981)	PP + attention control	Flooding Drug-aided flooding	21	Not determinable	2.78 .81	Not provided
Beck (1988)	PP (brief therapy)	Cognitive therapy	29	Not determinable	1.29	Not provided
Borden, Clum, & Broyles (1986)	WL	GIC Flooding	24	Not determinable	.44 .37	.40 .27
Gould, Clum, Shapiro, Weaver, & Blalock (1991)	WL	Bibliotherapy GIC	31	0 .44	1.49 .838	Not provided
Barlow, Craske, Cerny, & Klosko (1989)	WL PMR	Exposure + cog restr Exposure + cog restr	56	0 -.6	.442 (WL) -.381 (PMR) .523 (WL) -.186 (PMR)	Not provided
Ost (1988)	PMR	Applied relaxation	16	Not determinable	1.03	1.16
Borden, Clum, & Salmon (1991)	Panic education	GIC	19	Not determinable	.02	-.048
Williams & Rappaport (1983)	Exposure	Cognitive coping + exposure	20	-.61	-.33	-.64
Mavissakalian, Michelson, Greenwald, Kornblith, & Greenwald (1983)	Exposure	Cog restr + exposure	20	0	.91	-.41
Michelson, Mavissakalian, & Marchione (1988)	PMR Gradual exposure	Paradoxical intention	73	0 2	-.45 -.13	.04 .09
Telch, Agras, Taylor, Roth, & Gallen (1985)	DP + exposure	Imipramine Imipramine + exposure	27	Not determinable	-.402 .274	1.0 2.76
Mavissakalian & Michelson (1986)	DP + exposure (Progressive Practice)	Imipramine + flooding Imipramine + PP Flooding + DP	62	Not determinable	.093 .005 .114	Not provided

Study	Type of control	Type of treatment	n	Effect size		
				Dropout	Posttreatment	Follow-up
Zitrin, Klein, & Woerner (1980)	DP + exposure	Imipramine + exposure	50	0	.6506	Not provided
Hafner & Milton (1977)	DP + exposure	Propranolol	25	-.80	.289	Not determinable
Marchione, Michelson, Greenwald, & Dancu (1987)	Exposure	PMR + gradual exposure Cognitive therapy + exposure	14	Not determinable	.97 .97	Not provided
Emmelkamp & Mersch (1982)	Exposure	Exposure + self-instruction Cog restr		Not determinable	.0458 -.954	Not provided
Arnow, Taylor, Agras, & Telch (1985)	Relaxation	Couples communication & skills training plus exposure	24 24	Not determinable	.51	.44

Note. DP = drug placebo; MSD = methohexitone-assisted desensitisation; SSD = standard systematic desensitisation; MAOI = monoamine oxidase inhibitor; sup = support; psy = psychotherapy; WL = waiting list;
PP = psychological placebo; GIC = guided imaginal coping; cog restr = cognitive restructuring;
PMR = progressive muscle relaxation.

Meta analysis/systematic review extraction table

Author (s)	Research question	Review type Databases used Time period covered Data analysis	Study design Interventions Follow-up period	Numbers randomised Randomisation method Numbers incl in results analysis (Confirm ITT analysis or % included in results)	Total sample number Age (mean/SD/range) Male/female Ethnicity	Outcomes
<p>Bakker, A van Balkom, AJLM Spinhoven, P</p> <p>SSRIs vs. TCAs in the treatment of panic disorder: a meta- analysis</p> <p><i>Acta Psychiatr Scan</i> 2002; 106: 163-7</p>	<p>To update earlier meta- analysis: relative efficacy of SSRIs and TCAs in the treatment of panic disorder</p>	<p>Meta analysis</p> <p>Excerpta medica</p> <p>PsychInfo</p> <p>Index Medicus</p> <p>Searched up to 1999</p> <p>Cohen's d for within each of the treatment conditions</p> <p>Only effect sizes for complete data were used as almost no study presented intention to treat analysis</p> <p>Effect sizes - adjusted</p> <p>Random and non-random data pooled</p> <p>Mann-Whitney tests</p>	<p>43 studies with 53 treatment conditions (30 TCA and 23 SSRI)</p> <p>9 treatment conditions from open label studies</p> <p>(only those in italics are on our pharmacological intervention list - imipramine, clomipramine, desipramine, nortryptiline, fluvoxamine, fluoxetine, <i>paroxetine</i>, <i>citalopram</i>, sertraline)</p> <p>Weeks of treatment TCA: 9.7 (±4.7) SSRI: 9.6 (±2.7)</p> <p>[paroxetine 11 weeks mean; citalopram 8 weeks mean]</p>	<p>Total: 2367 included in results: 1804 dropout 23%</p> <p>TCA: 1059 at start 732 completed dropout 31%</p> <p>SSRI: 1308 at start 1072 completed dropout 18%</p> <p>[paroxetine 325 pre-test, 239 post- test, dropout 26%; citalopram 204 pre-test, 162 post-test, dropout 21%)</p> <p>Only effect sizes for completer data were used as almost no study presented intention to treat analysis</p>	<p>Age TCA: 34.4 (±4.1) yrs SSRI: 35.5 (±5.4) yrs</p> <p>Male female ratio: TCA: 0.5 SSRI: 0.51</p>	<p>Patients free of panic attacks at post-test</p>

Results: treatment, comparator data, dropouts (numbers/percentage and reasons), treatment emergent adverse events (whether spontaneous report or questioned by researcher/treating clinician), investigator's conclusions and reviewers conclusions if different from investigators

	TCA	SSRI	Paroxetine	citalopram
Patients free of panic attacks at post-test	60% (304/510)	55% (539/985)		
Cohen's d				
panic	1.46 (±0.84)	1.26 (±0.41)	1.17	1.92
(post-test) anxiety	1.27 (±0.58)	1.55 (±0.84)	not given	not given

[note: paper also reported effect sizes for depression and agoraphobia)

No statistically significant differences for effect size and percentage of patients free of panic attacks at post-test

Statistically significant difference in drop-out percentages – higher drop-out in TCA treated subjects (31% compared to SSRI treated subjects (18%), $p < 0.001$)

Author conclusion: SSRIs and TCAs have equal efficacy in the short-term treatment of panic disorder

[note: comparison of randomised and non-randomised treatment conditions did not result in any statistical difference, randomised data only: drop out rates 30% for TCA, 17% for SSRI: patients free of panic attack at post-test, 56% for TCA and 54% for SSRI; effect sizes were all in same range)

CBT/imipramine/combined imipramine + CBT

RCT extraction table

Author (s)	Study (placebo controlled, active comparator etc.	Type of intervention (pharmacotherapy & name of therapy) Length of study	Setting and location (primary/secondary care or other & country)	Numbers randomised Randomisation method Numbers incl in results analysis (Confirm ITT analysis or % included in results)	Inclusion criteria/ Exclusion criteria Exclusion of depression Permitted polypharmacy Washout period Substance misuse Concordance (compliance)	Mean age (years) Male/female (M/F) ratio Ethnicity	Follow-up period	Main outcome measures (extract data on primary outcome measure only and just note secondary outcome)
Barlow et al 2000 Cognitive-Behavioral Therapy, Imipramine, or their Combination for Panic Disorder: A Randomized Controlled Trial	Placebo and Active Comparator – multicentre study	Pharmacotherapy, Psychological therapy and mixed therapy. Study length = 12 weeks and 6 months maintenance (for responders) and 6 months follow-up 17 patients partook in an extended maintenance pilot.	Setting = anxiety research clinics	Total randomised = 326 Randomisation method = stratification according to site and presence of DSM-III-R diagnosis of PD Confirmed ITT analysis and analysis on completers given Numbers in groups Dropouts: CBT alone Imipramine Alone Placebo Alone CBT + imipramine CBT + placebo	Included if: passed diagnostic screening for principal diagnosis of PD with or without mild agoraphobia. Excluded if: Psychotic, bipolar, or significant medical illnesses, suicidal, significant substance abuse, contraindications to either treatment, prior nonresponse to similar treatments or concurrent competing treatment or pending disability claims Depression: Patients with comorbid unipolar depression were not excluded unless suicidal Permitted polypharmacy: up to 10 doses of BDZs (0.5mg of alprazolam-equivalent) in the 2 weeks before the first treatment visit and up to 20 doses during baseline and acute treatment combined. Washout period: stated but not duration Concordance	Mean age (SD) M/F ratio, ethnicity (% white race): For all patients 36.1 (10.7) 37.5/62.5, 90.8 CBT alone: 37.5 (10.9) 36.8/63.2, 89 Imipramine alone: 35.5 (9.7) 39.8/60.2, 89 Placebo alone: 34.2 (9.7) 25/75, 91.3 CBT + imipramine: 34.1 (11.4) 35.9/64.1, 95.3 CBT + placebo: 37.8 (11.3) 41.9/58.1, 90.3	6 months for 17 patients who sustained response to treatment during the maintenance phase	Panic Disorder Severity Scale (PDSS) – average item score PDSS response rate % CGI response rate
<p>Financial Disclosure: Dr Barlow has received research support from Pfizer and the National Institute of Mental Health and has served as a consultant for or received honoraria or royalties from Guilford Press, The Psychological Corporation, and Wyeth-Ayerst Pharmaceutical. Dr Gorman has received research support from Pfizer, Eli Lilly, and the National Alliance for Research on Schizophrenia and Depression and has served as a consultant for or received honoraria or royalties from Pfizer, Eli Lilly, Bristol-Myers Squibb, Wyeth Ayerst, SmithKline Beecham, AstraZeneca, Janssen, Organon, Forest, Parke Davis, Lundbeck, Solvay and Merck. Dr Shear has received research support from Eli Lilly, Pfizer, the National Institute of Mental Health, and SmithKline Beecham and has served as a consultant for or received honoraria or royalties from Pfizer, Glaxo, Hoffman-LaRoche, SmithKline Beecham, and Upjohn. Dr Woods has received research support from the National Institute of Mental Health and has served as a consultant for or received honoraria or royalties from Eli Lilly, Janssen, and Wyeth Ayerst.</p> <p>Funding/Support: This work was supported by the National Institute of Mental Health grant MH45964 (University of Pittsburgh School of Medicine); MH45965 (Boston University); MH45966 (Yale University School of Medicine); MH45963 and MH00416 (Senior Scientist Award) (Columbia University). Dr Barlow, Gorman, Shear and Woods have received research support from the National Institute of Mental Health. Imipramine and matching placebo were provided by Teva Pharmaceuticals USA.</p>								
<p>Results: treatment, comparator data, dropouts (numbers/percentage and reasons), treatment emergent adverse events (whether spontaneous report or questioned by researcher/treating clinician), investigator's conclusions and reviewers conclusions if different from investigators</p>								

Dosage: Imipramine 175-180mg/d by week 6; 214 to 239mg/d by week 12 – treatment sessions lasted 30 minutes
CBT (included interoceptive exposure, cognitive restructuring and breathing retraining): 11 sessions during 12 weeks of acute phase: treatment sessions lasted 50 minutes
(all results presented are intention-to-treat analysis)

Acute Phase	CBT alone	IMI alone	PL alone	CBT+IMI	CBT+PL	Total	P value
Numbers	77	83	24	65	63	312	
Responders	41	40	9	41	39		
Dropouts lack of efficacy	4	10	8	8	7		
Dropouts due to adverse events	0	11	0	2	0		
Non-compliance	4	2	0	0	2		
Unrelated to treatment	3	3	0	1	1		
Lost to follow-up	9	6	2	7	8		
PDSS average item score	1.14 (0.74)	1.05 (0.77)	1.52 (0.90)	0.68 (0.74)	0.99 (0.70)	1.06 (0.76)	.003
PDSS response rate %	48.7	45.8	21.7	60.3	57.1	50.0	.02
CGI response rate %	53.9	48.2	37.5	64.1	61.9	54.8	.10
Maintenance Phase							
Numbers completed	34	33	3	37	33	312	
Responders	32	31	3	36	31		
PDSS average item score	1.18 (0.86)	1.14 (0.87)	1.54 (0.83)	0.78 (0.86)	1.08 (0.79)	1.09 (0.86)	.001
PDSS response rate %	39.5	37.8	13.0	57.1	46.8	42.2	.003
CGI response rate %	42.1	37.8	13.0	56.3	50.0	43.3	.003
Follow-up Phase							
Numbers assigned	25	25	3	30	30	295	
Responders	23	15	3	15	25		
PDSS average item score	1.33 (0.93)	1.45 (0.83)	1.62 (0.77)	1.45 (0.90)	1.18 (0.92)	1.37 (0.89)	.12
PDSS response rate %	32.4	19.7	9.1	25.0	41.0	27.6	.01
CGI response rate %	31.9	19.7	13.0	26.3	41.0	28.0	.03
Pairwise comparison Acute (P)							
	IMI vs PL	CBT vs PL	IMI vs CBT	CBT+IMI vs CBT+PL	CBT+IMI vs CBT	CBT+IMI vs IMI	
PDSS average item score	.009	.02	.41	.34	.02	.15	
PDSS response rate %	.05	.03	.75	.86	.18	.10	
CGI response rate %	NA	NA	NA	NA	NA	NA	
Pairwise comparison Maintenance							
PDSS average item score	.04	.05	.72	.04	.004	.01	
PDSS response rate %	.02	.02	.87	.28	.04	.03	
CGI response rate %	.02	.01	.63	.59	.13	.03	
Pairwise Comparison Follow-up							
PDSS average item score	NA	NA	NA	NA	NA	NA	
PDSS response rate %	.34	.05	.09	.08	.43	.41	
CGI response rate %	.55	.11	.09	.12	.56	.41	

CBT alone and IMI alone vs placebo: Both superior to placebo for PDSS during acute and maintenance phase, and both had significantly fewer dropouts for lack of efficacy than placebo
CBT vs Imipramine: More dropouts in imipramine than CBT groups. Follow-up data trends favour CBT over Imipramine
Combined CBT+Imipramine vs Single treatment: Superior to CBT alone on PDSS average in both acute and maintenance phases and on the PDSS response rate for maintenance only. After treatment discontinuation (i.e. at 9 months, CBT alone, CBT+placebo continued to show evidence of superiority to placebo.
Conclusions: Both imipramine and CBT are better than pill placebo for treatment of PD. Imipramine produced a superior quality of response, but CBT had more durability and was somewhat better tolerated.

Appendix 2:

Combination compared with pharmacological interventions for panic disorder

Psychoeducation + SSRI (paroxetine)/SSRI (paroxetine)

RCT Extraction

Author (s)	Study (placebo controlled, active comparator etc.)	Type of intervention (pharmacotherapy & name of therapy) Length of study	Setting and location (primary/secondary care or other & country)	Numbers randomised Randomisation method Numbers incl in results analysis (Confirm ITT analysis or % included in results)	Inclusion criteria/ Exclusion criteria Exclusion of depression Permitted polycharmacy Washout period Substance misuse Concordance (compliance)	Mean age (years) Male/female (M/F) ratio Ethnicity	Follow-up period	Main outcome measures (extract data on primary outcome measure only and just note secondary outcome)
Dannon et al	Randomised study of psychoeducation in PD.	Psycho-education by use of the SIB brochure, with Paroxetine Paroxetine alone was the control group	Israeli specialist clinic	78 Not specified whether ITT or % completed study was used as basis for statistics	<u>Inclusion</u> DSM IV diagnosis PD or PDA <u>Exclusion</u> Age <18 Comorbid psychiatric diagnosis Psychological treatment in the last year Inability to sign consent form 16 patients had "mild" physical health problems IHD, Hypertension, NIDDM, and hypothyroidism	34.3 +/-12.2 47 women	12 weeks	HAM-A HRDS PSQ VAS
Results: treatment, comparator data, dropouts (numbers/percentage and reasons), treatment emergent adverse events (whether spontaneous report or questioned by researcher/treating clinician), investigator's conclusions and reviewers conclusions if different from investigators								
<p>Both control and active group showed equal improvement at 12 weeks; the level of improvement in symptoms from base line was statistically significant (which is to be expected) The difference between active and placebo group appears at the 3 week assessment when the active group showed a relatively earlier improvement, which was statistically significant</p> <p><u>The message:</u> The authors make the point that the outcome after 12 weeks was similar, but that it is important that the active group got better quicker. Compliance before the medication starts to have an effect (2 – 3 weeks) should theoretically lead to early drop outs, and the authors quote studies that support this view. Interestingly the authors do not quote drop outs in their study but ascribe the 6 patients who did drop out as being due to side effects of Paroxetine (they also do not say which groups they came from)</p> <p>If the authors are correct - that psycho-education works in the earlier stages and promotes compliance with medication and other interventions later – then it is significant. They propose that psycho-education type booklets should be available in a primary care setting, as it will promote compliance, and reduce referrals; whilst these are not evidence based they are suggestions that merit careful thought as examples of good practice that would make a significant difference to UK practice</p>								

Paroxetine + CBT/paroxetine/placebo

Panic Disorder

Author (s)	Study (placebo controlled, active comparator etc.)	Type of intervention (pharmacotherapy & name of therapy) Length of study	Setting and location (primary/secondary care or other & country)	Numbers randomised Randomisation method Numbers incl in results analysis (Confirm ITT analysis or % included in results)	Inclusion criteria/ Exclusion criteria Exclusion of depression Permitted polycharmacy Washout period Substance misuse Concordance (compliance)	Mean age (years) Male/female (M/F) ratio Ethnicity	Follow-up period	Main outcome measures (extract data on primary outcome measure only and just note secondary outcome)
Oehrberg, Christiansen, Behnke, Borup et al 1995	placebo	Type: paroxetine 20-60mg. Started at 10mg; increased to 20mg at week 2; increased thereafter according to tolerability and efficacy to upto 60mg Length: 3 weeks placebo (-3 – 0) 12 weeks intervention (0 – 12) 2 weeks placebo (12-14)	Setting: Location: Sweden 7 centres	Numbers: 120 randomisation:? concealment of allocation:? baseline comparability: yes numbers in results: analysis: both ITT and per protocol. Only ITT presented as similar	Inclusion: Age 18-70 Diagnosed panic disorder +/- agoraphobia (DSM-III-R) Exclusion: Severe depressive symptoms (>14 on Hamilton depression scale or diagnosis via DSM-III-R) Organic brain disease Drug/alcohol abuse Dementia schizophrenia Polypharmacy: Concurrent psychotropic drugs, MAOIs, benzodiazepines, anticoagulants not allowed	Age: Mean Paroxetine 37.7 Placebo: 37 years Range 21-69 Gender: Paroxetine 1: 4 Placebo: 1: 2.57 men: women ethnicity ?	Follow-up : 14 weeks assessments at: -3,-2,-1,0,1,2,3,4,6,9,12,14 weeks	Primary: Reduction in number of panic attacks Number of patients with ≥ 50% reduction in number of panic attacks (3,6,9,12 weeks) Paroxetine: 30,68,83, 82% Placebo: 20,40,52, 50% p-value: -, 0.006, 0.001, 0.001 Number of patients with reduction in number of panic attacks to 1 or 0: only significant at 12 weeks Paroxetine: 36% Placebo: 16% Mean change from baseline in number of panic attacks: NS secondary: reduction in Hamilton anxiety score response on Clinical Global Impression scale mean reduction on Zung Self-rating Scale for Anxiety
Results: treatment, comparator data, dropouts (numbers/percentage and reasons), treatment emergent adverse events (whether spontaneous report or questioned by researcher/treating clinician), investigator's conclusions and reviewers conclusions if different from investigators)								

<p style="text-align: center;">Other results:</p> <p>reduction in Hamilton anxiety score response on Clinical Global Impression scale mean reduction on Zung Self-rating Scale for Anxiety all reflected results of primary outcome. All statistically significant Dropouts: 13/120 Percentages Paroxetine: 5/ 60 (8%) Placebo: 8/ 60 (13%) Reasons Paroxetine: 1 lack of efficacy, 3 AE, 1 lack of compliance Placebo: 3 lack of efficacy, 3 protocol violation, 1 uncertain diagnosis</p> <p>treatment emergent adverse events: observed/spontaneous patient report/ response to open question vital signs and labs measured</p> <p>>1 adverse effect reported: Paroxetine: 77% Placebo: 55%</p> <p>Also counted AEs following discontinuation (weeks 12-14)</p> <p>investigators conclusions: paroxetine plus cognitive therapy was significantly more effective than placebo plus cognitive therapy in the treatment of panic disorder</p> <p>reviewers comments:</p>	<p><u>STUDY DESIGN</u> <i>objectives of trial sufficiently described:</i> yes <i>satisfactory statement of diagnostic criteria for trial:</i> yes <i>satisfactory statement of source of patients :</i> no <i>method of randomisation :</i> ? <i>concealment of allocation:?</i> <i>blinding:</i> pairs of visually identical tablets <i>delay between allocation and commencing intervention:</i> no <i>outcome measures: stated, appropriate, validity thereof:</i> yes; validity of outcome not clear <i>sample size calculation:</i> yes <i>post-intervention follow-up:</i> 2 weeks</p> <p><u>STUDY CONDUCT</u> <i>comparability of groups re baseline characteristics:</i> fully described <i>losses to follow-up:</i> none <i>numbers of non-completers of intervention:</i> small <i>description of non-completers:</i> no</p> <p><u>ANALYSIS AND PRESENTATION</u> Failed to report primary results in numerical form or give confidence intervals</p> <p style="text-align: center;">reviewers conclusions:</p> <p>paroxetine plus cognitive therapy was significantly more effective than placebo plus cognitive therapy in the treatment of panic disorder short follow-up substantial improvement in placebo group</p> <p>level of evidence: 1+</p>
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CBT + SSRI (paroxetine)/CBT + placebo

RCT extraction table

Author (s)	Study (placebo controlled, active comparator etc.)	Type of intervention (pharmacotherapy & name of therapy) Length of study	Setting and location (primary/secondary care or other & country)	Numbers randomised Randomisation method Numbers incl in results analysis (Confirm ITT analysis or % included in results)	Inclusion criteria/ Exclusion criteria Exclusion of depression Permitted polypharmacy Washout period Substance misuse Concordance (compliance)	Mean age (years) Male/female (M/F) ratio Ethnicity	Follow-up period	Main outcome measures (extract data on primary outcome measure only and just note secondary outcome)
Kampman, Keijsers	Placebo controlled Double blind	Type: CBT + paroxetine 40mg vs CBT + placebo Length: initial period of 15 weeks of CBT(phase 1). 4 week break. Non-responders then proceed to 8 week RCT (phase 2)	Setting: Outpatient clinic for anxiety disorders and a university outpatient clinic Location Holland	Numbers: see below randomisation: ? concealment of allocation: ? numbers in results: 38. only completers analysed	Inclusion: Age 18-65 Diagnosed panic disorder +/- agoraphobia (DSM-IV) Exclusion: schizophrenia Organic brain disease Mental retardation Drug/alcohol abuse Suicidal ideation Pregnancy/intention thereof Polypharmacy: antidepressant discontinued > 2weeks prior. Stable benzodiazepine dose	Age: ? Gender: ? Ethnicity ?	Follow-up : Every 2 weeks during treatment. Assessment at 8 weeks of treatment. Nil beyond completion	Primary: 1) frequency of catastrophic agoraphobic cognitions: Dutch ACQ 2)Agoraphobic avoidance:: Dutch MI *(mobility index) 3)fear and frequency of physical panic sensations : Dutch BSQ (body sensations questionnaire) 4) global state of phobic symptoms and general discomfort: fear questionnaire (FQ-GA)* 5) distress or anxiety: Dutch ADS* 6) proportion of patients panic free after treatment *: significantly greater improvement in paroxetine group than placebo
Numbers 32 dropouts 161 entered phase 1 129 63 effective 66 failed 6 excluded(pregnancy) 60 eligible 17 refused 43 entered phase 2 22 CBT+ paroxetine 21 CBT + placebo 3 drop-outs 2 drop-outs								

Results: treatment, comparator data, dropouts (numbers/percentage and reasons), treatment emergent adverse events (whether spontaneous report or questioned by researcher/treating clinician), investigator's conclusions and reviewers conclusions if different from investigators

Dropouts: 3+2

Percentages

Placebo 9%

Paroxetine:13.6%

Reasons "adverse side-effects". Not detailed

treatment emergent adverse events: not described

investigators conclusions: patients failing to respond to CBT may benefit from an SSRI as second treatment modality

reviewers comments:

STUDY DESIGN

objectives of trial sufficiently described: all very unclear whether a trial of "CBT+/- subsequent paroxetine" or a trial of " paroxetine in group of non-CBT responders"

satisfactory statement of *diagnostic criteria* for trial: yes

satisfactory statement of *source of patients* :yes

method of randomisation :unclear

concealment of allocation: unclear

blinding: dummy drug. Presumed visually identical

delay between allocation and commencing intervention: timing unclear. About a month delay for assessing response to phase 1

outcome measures: stated, appropriate, *validity* thereof: stated and referred to. Validity is mentioned and referenced. "Dutch versions" used.

sample size calculation: none

post-intervention follow-up: none

STUDY CONDUCT

comparability of groups re baseline characteristics: age and sex. Baseline difference in ADS. Baseline difference in co-morbid disorders.

losses to follow-up: none.

numbers of *non-completers* of intervention: 5 drop-outs.

description of non-completers: none

adverse effects poorly described

ANALYSIS AND PRESENTATION

Very scant data presentation. Poor description of methods.

reviewers conclusions:

small numbers. Multiple losses. Baseline non-comparability. Randomisation not clear when or how. Short treatment duration. Multiple primary outcomes: some showed effect, some not. Small treatment effect. Statistics poorly demonstrated

level of evidence:

sign 1-

RCT extraction table

Author (s)	Study (placebo controlled, active comparator etc.)	Type of intervention (pharmacotherapy & name of therapy) Length of study	Setting and location (primary/secondary care or other & country)	Numbers randomised Randomisation method Numbers incl in results analysis (Confirm ITT analysis or % included in results)	Inclusion criteria/ Exclusion criteria Exclusion of depression Permitted polypharmacy Washout period Substance misuse Concordance (compliance)	Mean age (years) Male/female (M/F) ratio Ethnicity	Follow-up period	Main outcome measures (extract data on primary outcome measure only and just note secondary outcome)
Stein, M. B., Ron, N. G., Walker, J. R., Chartier, M. J., & Graham, R. 2000, <i>Psychiatry Research</i> , vol. 94, no. 3, pp. 191-200.	Placebo Two armed study randomised SSRI + CBT or Placebo +CBT	Type: Combination therapy SSRI (paroxetine) + vbCBT paroxetine (flexible dosing 10-50 mg/day) vbCBT 45 min and 30 mins sessions at weeks 5 and 7 respectively supplemented with educational and directive reading materials and a 'booster' session at week 10. Note: there was no CBT before week 5. Length: 10 weeks	Anxiety Disorders Clinic, Winnipeg, Canada	Numbers: 33 17 randomized to a placebo 16 to paroxetine Numbers In results: 31 concealment of allocation: Y baseline comparability: Y Double blinded Analysis was on the basis of last observation carried forward for non-completers or incomplete data.	Inclusion: Age 18-65 DSM-IV diagnosis with severity rating at least 4 on CGI At least 4 panic attacks in preceding 4 weeks Exclusion: Medical disorder(s) related to panic disorder; other severe psychiatric disorders; suicide risk psychological treatment Polypharmacy: concurrent treatment with psychotropic medication excluded Washout period of 1 week where both groups received a placebo. Subsequently, both groups received 10 mg of paroxetine for 4 days. (The view of the authors was that this would help with concealment as placebo group would experience/report side-effects)	Age: Mean 33.8 Placebo 34.8 Paroxetine 32.7 Gender: Placebo 76% female Paroxetine 69% female Ethnicity: ?	Follow up: None	Primary Measure Proportion of subjects considered responders on the Clinical Global Impression Scale of Change (CGI-C) (7 point scale from 'very much improved' to 'very much worse') 'Responders' defined as those rated 'much' or 'very much improved' Both a patient rated and clinician rated version were administered at 5 and 10 weeks. Secondary Measure Frequency of panic attacks as recorded in diary

Results: treatment, comparator data, dropouts (numbers/percentage and reasons), treatment emergent adverse events (whether spontaneous report or questioned by researcher/treating clinician), investigator's conclusions and reviewers conclusions if different from investigators

Primary: No significant difference in responders on CGI-C-CI scale (placebo 12/16 {75%}; paroxetine 13/14 [93%])

Benefit of SSRI administration visible with CGI-C 'very much improved' criterion :

CGI-C-CI (placebo 3/16 [19%]; paroxetine 7/14 [50%])

CGI-C-Pt (placebo 2/16 [13%]) achieved high end-state functioning vs. paroxetine 9/15 [60%]

Secondary:

Significant difference in panic free subjects at week 10 (placebo 4/16 [25%] ; paroxetine 12/15 [80%])

No significant difference in two groups experiencing zero attacks at week 10

Other results:

Patients in both groups (i.e. vbCBT+paroxetine; vbCBT+placebo) improved similarly and substantially on most measures during the 10 weeks of acute treatment.

At week 10 the proportion of panic-free patients was significantly higher in the paroxetine-treated group than in the placebo group (80 vs 25%; $P < 0.007$) as was the proportion of subjects who rated themselves as 'very much improved' at week 10 (60 vs 13%; $P < 0.017$).

Dropouts: 2/33

Paroxetine 1

placebo 1

Reasons: ?

Treatment emergent adverse events:

Investigator's conclusions:

Small sample size thus substantial possibility of type II error. Addition of an SSRI failed to improve outcomes across most measures of symptoms and disability. Proportion of subjects reporting zero full panic attacks at endpoint significantly favored paroxetine plus vbCBT combination over placebo plus vbCBT.

Appendix 3:

Pharmacological interventions for panic disorder

Pharmacological interventions compared with pharmacological interventions

Meta-analyses, systematic reviews and other reviews

SSRIs/TCAs

Meta analysis/systematic review extraction table

Author (s)	Research question	Review type Databases used Time period covered Data analysis	Study design Interventions Follow-up period	Numbers randomised Randomisation method Numbers incl in results analysis (Confirm ITT analysis or % included in results)	Total sample number Age (mean/SD/range) Male/female Ethnicity	Outcomes
Otto et al 2001	An effects size analysis providing initial comparison of SSRIs vs older agents (indirect comparison) for the treatment of panic disorder	Systematic review PsychLIT, MEDLINE, discussions with colleagues and examination of ref. Sections of related articles Time period: not stated; earliest study was 1993 and latest 1998	Double-blind, placebo-controlled Interventions: SSRIs incl paroxetine, fluoxetine, fluvoxamine, sertraline, citalopram Follow-up period: not stated	Not stated No confirmation of ITT analysis	Total sample = 1741 Age: not stated Male/female ratio not stated Ethnicity not stated	Effect Size on all dependent measures Dropouts Year of publication Changes in sample responsiveness over time using panic-free rate for patients in placebo
<p>Results: treatment, comparator data, dropouts (numbers/percentage and reasons), treatment emergent adverse events (whether spontaneous report or questioned by researcher/treating clinician), investigator's conclusions and reviewers conclusions if different from investigators</p> <p>Effect Sizes: refer to table on page 3 Mean effect size of $d=0.55$ for SSRIs Panic frequency effects size of 0.38 based on 8 studies. Authors note that larger studies associated with lower effect sizes ($R=0.72$, $F_{10.9}$, $df=1$, 10, $p<0.009$). When SSRI and imipramine studies weighted in accordance with heterogeneity in sample size, effect sizes for overall ES and panic frequency were 0.47 for SSRIs and 0.37 for imipramine. Using unpaired t tests, there were no significant differences between imipramine (included for illustrative purposes only) and the SSRIs.</p> <p>Study Dropouts: Mean dropout for SSRIs = 19.9%, $SD_{10.9}$. No significant difference with comparison conditions. When data pooled across all studies, mean dropout rate for SSRIs = 24.6%</p> <p>Year of publication: Funnel plot revealed a strong negative association between sample size and effect size. Sample size confounded with the year of study publication ($R=0.76$, $F=13.4$, $df=1$, 10, $p<0.004$). More recently published studies associated with smaller SSRI effect sizes ($R=0.82$, $F=20.1$, $df=1$, 10, $p<0.002$). This result not affected by treatment under review.</p> <p>Changes in sample responsiveness over time using panic-free rate for patients in placebo No significant association between year of publication and treatment responsibility ($R=0.41$, $F=1.40$, $df=1$, 8 $p<0.28$)</p> <p>Authors conclusion: An effect-size analysis of controlled studies of treatment for panic disorder revealed no significant differences between SSRIs and older antidepressants in terms of efficacy or tolerability in short-term trials. An inverse relationship was evident between sample size and effect size for SSRIs. Early studies of small samples may have led to initial overestimations of the efficacy of SSRIs for panic disorder</p> <p>Reviewers comments: This is an extremely well done, clearly focused and presented the review but lack of specification of ITT analysis of included studies detracts from reliability of findings. All steps of the review process are clearly explained. Bias in favour of the treatment is indicated by lack of evidence of harms. However, analysis of efficacy outcomes only revealed no significant difference and this bias is thus eliminated.</p>						

SSRIs (paroxetine, fluvoxamine, citalopram)/TCAs (clomipramine, imipramine) Benzodiazepines (diazepam, alprazolam)

Meta analysis/systematic review extraction table

Author (s)	Research question	Review type Databases used Time period covered Data analysis	Study design Interventions Follow-up period	Numbers randomised Randomisation method Numbers incl in results analysis (Confirm ITT analysis or % included in results)	Total sample number Age (mean/SD/range) Male/female Ethnicity	Outcomes
11978 Baldwin & Birtwistle The side effect burden associated with drug treatment of panic disorder In <i>J Clin Psychiatry</i> 1998; 59 (suppl 8)	A review of the incidence of side-effects in placebo-controlled clinical trials of drug therapy in patients with panic disorder.	Systematic review without meta-analysis Databases used: MEDLINE Tim period: 1992 to 1997 Data analysis	Design stated as 'placebo-controlled studies' Follow-up period: stated for SSRIs as 36 weeks	Numbers randomised: TCAs: N=122 SSRIs: N=367 BDZ (including alprazolam) = N=235 It is not stated whether included studies performed and ITT analysis on results	Total sample (of those included in this review) = 724 Age: not stated Male/female: not stated Ethnicity: not stated	Percentage of patients experiencing treatment emergent side-effects.
Results: treatment, comparator data, dropouts (numbers/percentage and reasons), treatment emergent adverse events (whether spontaneous report or questioned by researcher/treating clinician), investigator's conclusions and reviewers conclusions if different from investigators						

NOTE: Results are presented here of those studies examining Pharmacotherapies under consideration for conclusion in the NICE Anxiety Guidelines including IMIPRAMINE, FLUVOXAMINE, PAROXETINE, CITALOPRAM, CLONAZEPAM AND DIAZEPAM. Treatment emergent side effects of other, black or non-listed drugs have not been considered including, Alprazolam, Clomipramine, Ritalin and Lofepramine.

Some of the tables present results of included drugs in comparison to one of the black/non-listed therapies as well as placebo – hence their listing. The review considers each drug by group in turn.

TCAs – Imipramine (and clomipramine)

Results are presented of a 12 week, double-blind, placebo-controlled comparison of imipramine and clomipramine (Modigh et al) (Modigh, Westberg, & Eriksson 1992). Although there are significantly more reports of side-effects in the active treatment groups vs placebo patients and significantly more in the imipramine vs the clomipramine patients, the type of symptoms are indicative of panic disorder rather than drug-effects.

SEE TABLE 1 (BELOW)

SSRIs

Three SSRIs included in the Guidelines are reviewed in this paper: Fluvoxamine (date derived from the following papers: (Bakish et al. 1996; Black et al. 1993; de Beurs et al. 1995)); Paroxetine (date derived from (Oehrberg et al. 1995) (Lecrubier et al. 1997), (Lecrubier & Judge 1997; Whittal, Otto, & Hong 2001)) and Citalopram (data derived from (Wade et al. 1997))

Fluvoxamine

Two studies comparing psychological treatment with fluvoxamine (Black, Wesner, Bowers, & Gabel1993; de Beurs, van Balkom, Lange, Koele, & van Dyck1995) revealed that in the first 8 week study in which a flexible dose up to 300mg per day was administered (Black et al 1993) participants in the fluvoxamine arm experienced significantly more side effects than the psychological (cognitive) therapy arm ($p \leq .005$) in the first week and significantly more than placebo in the first 4 weeks of treatment ($p \leq .01$). Placebo patients were noted as experiencing significantly more side effects than the psychological therapy group. In the second, 12-week study (de Beurs, van Balkom, Lange, Koele, & van Dyck1995), it was recorded that only headache in the fluvoxamine + in vivo exposure recipient group had a significantly greater score recording side-effects than the placebo plus exposure group ($p = .05$). It was also noted that all side effects resolved with continuation of treatment although it is not stated within what timeframe.

In a comparison of fluvoxamine with imipramine (Bakish, Hooper, Filteau, Charbonneau, Fraser, West, Thibaudeau, & Raine1996) and placebo, dry mouth was experienced in about 80% of imipramine-treated patients. Side-effects reported more often in the fluvoxamine group were insomnia and a ‘funny’ taste in the mouth. It was noted that the investigators considered fluvoxamine to be better tolerated than imipramine with fewer side effects.

Paroxetine

Three separate studies recorded the side effects of Paroxetine. One 12 week study (Oehrberg, Christiansen, Behnke, Borup, Severin, Soegaard, Calberg, Judge, Ohrstrom, & Manniche1995), in which subjects received either cognitive therapy plus Paroxetine (up to 20mg/day) or cognitive therapy plus placebo, the most commonly reported side-effects were nausea (23% paroxetine group, 12% placebo group), sweating (23% Paroxetine grp vs 5% placebo) and headache (22% paroxetine grp vs 23% placebo). Another study (Lecrubier, Bakker, Dunbar, & Judge1997) comparing paroxetine up to 60mg/day to clomipramine (up to 150mg/day) and placebo recorded that paroxetine was better tolerated than both clomipramine and placebo. Results are presented in the table and it is noted that side –effects are significantly greater in the clomipramine group at $p = .002$. Results are also presented of a study in which those involved in this 12 week study could elect to partake in a longer term study (Lecrubier & Judge1997). Results show that side-effects decrease in the long term extension study in the Paroxetine group.

Table 1. Incidence (% of patients) of Side Effects Experienced Significantly ($p, .05$) More Frequently by Patients with Panic Disorder Treated for 12 Weeks With Clomipramine (25-200 mg daily), or Imipramine (50-250 mg daily) Than With Placebo*

Side effect	% of Patients			p Value
	Clomipramine (N=22)	Imipramine (N=29)	Placebo (N=17)	
Dry mouth	100	96	67	.0004
Sweating	77	89	27	.0001
Orthostatism	77	82	33	.002
Obstipation	64	71	27	.01
Headache	14	46	47	.04

*Data from reference 5.

Table 2. Percentage of Patients With Panic Disorder Experiencing Emergent Side Effects During Acute (12 weeks*) and Chronic (36 weeks†) flexible-Dose Treatment With Paroxetine (20-60 mg daily), Clomipramine (50-150 mg daily), or Placebo

Side effect	% of Patients		
	Paroxetine (N=123)	Clomipramine (N=121)	Placebo (N=123)
12 Weeks			
At least 1 side effect	73	89 ^a	68
Sweating	22	30	12
Dry mouth	20	50	14
Nausea	20	31	15
Headache	16	17	18
Insomnia	13	10	7
Dizziness	11	18	9
Asthenia	11	14	4
Diarrhea	11	3	4
Constipation	8	17	8
Somnolence	7	11	6
Tremor	5	25	1
Abnormal ejaculation ^b	26	24	2
Impotence ^b	4	15	0
36 Weeks			
At least 1 side effect	62	76	51
Headache	10	11	13
Sweating	10	21	7
Dry mouth	7	14	4
Dizziness	12	11	0
Weight gain	6	14	0
Abnormal ejaculation ^b	12	4	0

*From reference 12, with permission

†From reference 13, with permission

^ap = .002 vs paroxetine

^bGender specific, with percentage calculated for male patients

Citalopram

Treatment emergent side-effects were recorded in an 8-week study comparing citalopram (at 3 dose levels: 10-20mg, 20-30mg and 60-60mg/day) and clomipramine to placebo. Sweating and anorgasmia were significantly more common in the citalopram treatment group than in the placebo group. A dose-related response was noted in the side-effect of anorgasmia. There were more side effects in the clomipramine group than placebo. Citalopram was better tolerated than Clomipramine.

SEE TABLE 3 BELOW

Benzodiazepine

An 8 week study comparing Diazepam with Alprazolam and placebo recorded that there were no significant differences in treatment-emergent side effects between treated patients.

SEE TABLE 5 (BELOW)

Conclusion: The authors stated that the evidence points most favourably to SSRIs in terms of side effect profile for patients with panic disorder.

Reviewers conclusion: As no direct head-to-head comparisons were made between SSRIs and Benzodiazepines or between TCAs and Benzodiazepines, a conclusion such as that reached by the reviewers is very tentative. Only one comparison is made between fluvoxamine and imipramine.

Panic disorder and generalised anxiety disorder (full guideline) appendices: January 2004

Table 3. Percentage of Patients Experiencing Treatment-Emergent Side Effects During 12 Weeks of Fixed-Dose Treatment With Citalopram (10-15 mg, 20-30 mg, or 40-60 mg), Clomipramine (60-90 mg) or Placebo*

Side Effect	Citalopram		Clomipramine		Placebo (N=96)
	10-15 mg (N=97)	20-30 mg (N=95)	40-60 mg (N=89)	60-90 mg (N=98)	
Headache	33 ^a	26	29 ^a	16	28
Nausea	27	28	29	30	18
Dry mouth	12 ^a	12 ^a	17 ^a	33 ^b	15
Sweating	10	18 ^b	16	19 ^b	7
Dizziness	9	14	7 ^a	18 ^b	6
Insomnia	8	11	7	16	7
Abdominal pain	4	5 ^a	7 ^a	0 ^b	5
Tremor	3 ^a	7	2	17 ^b	5
Constipation	1	3	2	7	2
Anorgasmia	2	9 ^b	10 ^b	10 ^b	0

*From reference 14, with permission

^aSignificantly different from clomipramine

^bSignificantly different from placebo

Table 5. Percentage of Patients With Panic Disorder Experiencing Treatment-Emergent Side Effects During 8 Weeks of Flexible-Dose Treatment With Alprazolam, Diazepam, or Placebo*

Side Effect	Diazepam (N=81)	Alprazolam (N=77)	Placebo (N=77)
CNS			
Drowsiness	84	77	42 ^a
Fatigue	57	44	42
Impaired thinking	44	38	22 ^a
Memory problems	40	34	31
Neuromuscular			
Incoordination	56	40	17 ^a
Slurred speech	32	23	5 ^a
Genitourinary			
Urinary difficulty	17	16	10
Menstrual irregularity	18	12	6
Libido decrease	19	13	5 ^a
Libido increase	19	8	4 ^a
Sexual dysfunction	7	3	1
Gastrointestinal			
Appetite decrease	22	20	20
Appetite increase	32	30	14 ^a
Weight gain	24	17	14
Weight loss	12	14	8

ap < .05 vs active treatment

*From reference 24, with permission

SSRIs (paroxetine)/TCAs (clomipramine)

Systematic Review

Author (s)	Research question	Review type Databases used Time period covered Data analysis	Study design Interventions Follow-up period	Numbers randomised Randomisation method Numbers incl in results analysis (Confirm ITT analysis or % included in results)	Total sample number Age (mean/SD/range) Male/female Ethnicity	Outcomes
Wagstaff, et al 2002 Paroxetine Use in Psychiatric Disorders	Efficacy of paroxetine	Review of studies of patients with major depressive disorder, dystymia, OCD, PD, social anxiety disorder, GAD, PTSD and social phobia who received Paroxetine. Medical literature published in any language since 1980 to 21/1/2002 on paroxetine, identified using Medline and EMBASE supplemented by Adisbase. Additional references were identified from the reference lists. Bibliographic information, including contributory unpublished data was also requested from the company developing the drug.	Inclusion was based on the methods section with, when available, large well controlled trails with appropriate statistical methodology preferred. However papers on anxiety disorders predominately focussed on short-term placebo-controlled trial of double blind RCT's. Most studies included a placebo controlled 1-3 week run-in period before randomisation. Trials were 8-32 weeks	ITT in the main and it is noted where not	2000 patients Included in studies if met the DSM-IV criteria and generally excluded if had other axis I disorders or had recently been or currently taking psychotropic medication.	Data are from primary efficacy end-points only including <ul style="list-style-type: none"> • Change from baseline in HARS • Proportion of patients experiencing relapse (defined as an increase in CGI severity of illness of at least 2 points to GE 4 at week 12) in long term trials. Data for secondary efficacy endpoints only included if provide valuable additional information.

Results: treatment, comparator data, dropouts (numbers/percentage and reasons), treatment emergent adverse events (whether spontaneous report or questioned by researcher/treating clinician), investigator's conclusions and reviewers conclusions if different from investigators

Efficacy

Vrs. Placebo

Paroxetine (20-50 mg/day) significantly improved symptoms of anxiety (measured using HARS total score) compared with placebo in 2 x 8 week randomised double blind trials involving 324 (ITT) and 426 (evaluable) outpatients. In a third 8 week trial, the reduction in HARS total score from baseline was numerically greater with paroxetine (20-50 mg/day) than placebo. In a 32 week relapse prevention study, significantly fewer patients receiving paroxetine relapsed (defined as an increase in CGI severity of GE 2 points to a score of at least 4 or withdrawn due to lack of efficacy) than those receiving a placebo. (10.9 vrs 39.9%)

Vrs. Imipramine and 2'chlordesmethydiazepam

Paroxetine (20 mg/day) was similar in efficacy to imipramine (50-100 mg/day) but greater than 2'chlordesmethydiazepam (3-6 mg/day) in a small (evaluable n=63) randomised trial. In a 32 week relapse prevention trial, significantly fewer in the paroxetine group (10.9%) relapsed than in the placebo group(39.9%)

SEE TABLE BELOW FOR DETAIL OF STUDIES

Tolerability

In patients receiving paroxetine for various psychiatric disorders, the most common adverse events (incidence GE 5%) included nausea, sweating, headaches, dizziness, somnolence, constipation, asthenia and sexual dysfunction. Adverse events were generally mild and, in the case of nausea and dizziness, transient.

The incidence of abnormal ejaculation among patients with GAD & PD ranged from 21-28% with a dosage range from 10-60 mg/day. This is commonly associated with all SSRI's.

All SSRI's have been implicated in the development of serotonin syndrome, a potentially life threatening complication. There have been reports of serotonin syndrome developing when paroxetine was coadministered with MAOI's or other SSRI's or after a switch from another SSRI without a washout period.

A meta-analysis of 39 studies of for treatment of depression showed a statistically significant lower proportion of patients receiving paroxetine (64%) experienced adverse events with an incidence of > 1% than those receiving Clomipramine (77% p=0.02) or another TCA (77% p<0.001). There was a trend toward a lower incidence of withdrawal due to adverse events with paroxetine compared to TCA's which reached significance with Clomipramine (ref 38)

Paroxetine has been compared to other SSRI's in depression studies and has a similar tolerability profile.

SSRI's also seem to be generally better tolerated than TCA's in the elderly with equal tolerance among the SSRI's based on depression studies.

Dosage

UK prescribing				
Recommended dosage(mg/day)	Initial dosage (mg/day)	Titration(mg/day)	Max dosage(mg/day)	Maintenance
20	20	10 (after 2 wks)	50	Up to 12 weeks, no evidence that dosages GE 20 mg/day impart an additional benefit. continuation at lowest effective dose may be considered with regular re-assessment

Wagstaff Studies Reviewed for GAD

Efficacy of paroxetine (PAR) compared with placebo (PL), imipramine (IMI) or % chlordesmethyldiazepam (CHL) in adult patients with generalised anxiety disorder (defined using DSM-IV criteria) in short-term randomised trials. Placebo-controlled trials were double blind (Data are for primary efficacy endpoints)

Reference	Duration (wk)	No of patients randomised (evaluable)	Treatment(mg/day)	HARS total score	
				Baseline (mean)	reduction from baseline
Versus placebo Bellew et al ^{[48]a}	8	197 (143)	PAR 40	23.3	13.9 ^{***}
		189 (143)	PAR 20	23.8	13.8 ^{***}
		180 (140)	PL	23.9	10.7
Hewett et al [40]	8	181	PAR 20-50	NR	12.6 ^b
		183	PL	NR	11.3 ^b
Pollack et al	8	161	PAR 20-50 (mean 26.8)	24.2	12.1 ^{**}
		163	PL	24.1	9.5 ^b
Versus imipramine and % chlordesmethyldiazepam Rocca et al ^[50]	8	30 (25)	PAR 20	26.7	15.6 [†]
		26 (18)	IMI 50-100	24.7	13.9 [†]
		25 (20)	CHL 3-5	24.7	11.8

a Preliminary data were presented in a poster

b Data were estimated from a graph

OSM IV + Diagnostic and Statistical Manual or Mental Disorders fourth edition: HARS = Hamilton Anxiety Rating Scale: *p <0.05

p < 0.01. *p < 0.001 vs. PL; † = p < 0.05 vs. CHL

Benzodiazepines/SSRIs/tricyclics

Meta analysis/systematic review extraction table – SSRI's

Author (s)	Research question	Review type Databases used Time period covered Data analysis	Study design Interventions Follow-up period	Numbers randomised Randomisation method Numbers incl in results analysis (Confirm ITT analysis or % included in results)	Total sample number Age (mean/SD/range) Male/female Ethnicity	Outcomes
Den Boer, J Pharmacotherapy of Panic Disorder: Differential Efficacy from a clinical viewpoint. 1998	Efficacy of benzodiazepines compared and to SSRI's, TCAs	Controlled clinical studies from Medline 1966 to date (?1998) for Panic disorder				Freedom from panic attack. Reduction of panic attack frequency and ability to attenuate global anxiety (HAM-A, SCL-90, Clinical Anxiety Scale), depressive symptomatology (HAM-D, Montgomery-Ashberg and Zung Self rating) , agoraphobic avoidance (SCL-90, Overall Phobia Scal, Marks Matthews Phobia Scale, Fear Questionnaire and CGI)and overall impairment (Sheehan Disability Scale).
<p align="center">Results: treatment, comparator data, dropouts (numbers/percentage and reasons), treatment emergent adverse events (whether spontaneous report or questioned by researcher/treating clinician), investigator's conclusions and reviewers conclusions if different from investigators</p> <p>This review has a great deal comparing different classes of drugs.</p> <p>Paroxetine – combined over 700 patients have been treated from 10-36 weeks. After acute treatment 36-86% of treated group were panic free whereas 16-0% of placebo group were. Paroxetine compared to clomipramine - 51% of Paroxetine and 37% of clomipramine were panic free. Reduction in global anxiety demonstrated in studies of Paroxetine comparable to that of clomipramine. SSRI's improved depressive symptoms compared with placebo Comparative data between SSRI's (Citalopram and Paroxetine) and clomipramine showed no statistically significant difference in improvement of depressive symptoms. All were equally efficacious. Paroxetine and clomipramine produced similare reductions in overall phobia scores using Marks Sheehan Phobia Scale during 12 week acute phase and during the extension of the study. No differences between the two treatment groups were found. Comparing Paroxetine and clomipramine, both showed similar improvements in the short in work, social and family life compared to the placebo. Subjects continued to improve in the long term.</p> <p>Citalopram – With a 20-30 mg/day dose 58% of Citalopram group, 50% of clomipramine group and 32% of placebo group were panic free. Citalopram and clomipramine showed equal efficacy in reducing global anxiety in a large multi centred study. Comparative data between SSRI's (Citalopram and Paroxetine) and clomipramine showed no statistically significant difference in improvement of depressive symptoms. All were equally efficacious.</p> <p>NOTE: good table on p. 31 which could be distributed</p> <p>Author's conclusion – the anti-depressants have been shown to be more effective than the benzodiazepines in reducing depression, and at least as effective in improving anxiety, agoraphobic avoidance and overall impairment. Does not comment on comparison of freedom from panic attacks.</p>						

SSRIs

Author (s)	Research question	Review type Databases used Time period covered Data analysis	Study design Interventions Follow-up period	Numbers randomised Randomisation method Numbers incl in results analysis (Confirm ITT analysis or % included in results)	Total sample number Age (mean/SD/range) Male/female Ethnicity	Outcomes
Baldwin, D & Birtwistle J “Selective serotonin re-uptake inhibitors in anxiety disorders: room for improvement” 2000	Efficacy of SSRI’s in the treatment of common anxiety disorders including GAD and PD as well as OCD and PTSD	Medline Express and Embase January 1985 to June 1999. Searched for Citalopram, Fluoxetine, Paroxetine, Sertraline and zimelidine (Note zimelidine has subsequently been withdrawn because of side-effects)	Searched only for double blinded RCT’s. Recent studies published as abstracts were accepted.			
<p>Results: treatment, comparator data, dropouts (numbers/percentage and reasons), treatment emergent adverse events (whether spontaneous report or questioned by researcher/treating clinician), investigator’s conclusions and reviewers conclusions if different from investigators</p> <p>The authors could find no studies for treatment of patients with SSRI’s in their searches. They await the results of the paroxetine study.</p>						

SSRI (citalopram) vs TCA (clomipramine)

RCT extraction table

Author (s)	Study (placebo controlled, active comparator etc.)	Type of intervention (pharmacotherapy & name of therapy) Length of study	Setting and location (primary/secondary care or other & country)	Numbers randomised Randomisation method Numbers incl in results analysis (Confirm ITT analysis or % included in results)	Inclusion criteria/ Exclusion criteria Exclusion of depression Permitted polypharmacy Washout period Substance misuse Concordance (compliance)	Mean age (years) Male/female (M/F) ratio Ethnicity	Follow-up period	Main outcome measures (extract data on primary outcome measure only and just note secondary outcome)
Wade AG 1997 The effect of citalopram in panic disorder	Double-blind placebo and comparator controlled flexible dose within a fixed dose range	Subjects were randomised to treatment with either 1. placebo, 2. clomipramine 60 or 90 mg/day, or 3. citalopram 10mg/day with the option of increasing to 15 mg/day if efficacy not seen, or 4. citalopram titrated over 3 weeks to 20mg/day with the option of increasing to 30 mg/day if efficacy not seen, or 5. citalopram titrated over 3 weeks to 40 mg/day with the option of increasing to 60 mg/day day if efficacy not seen. 8 week study	22 centres in Finland, Sweden, the Netherlands and the UK	N= 475 patients randomised (ITT population) 115 of these failed to complete the study ITT population was defined as all patients who received a tablet of double blind medication, and the efficacy population was defined as randomised patients who were treated for GE 28 days and received no prohibited medication.	Inclusion criteria: Patients with PD, with or without agoraphobia aged 18-65 years who scored LT 22 on Montgomery-Asberg depression rating scale (MADRS) and fulfil DSM-III-R criteria for PD. They must have suffered at least one panic attack/week with at least 3 (DSM-II-R) symptoms during the 3 weeks immediately before entering the study and at least one panic attack during the one week screening period of the study. Exclusion criteria: pregnancy (intended or actual), depression, organic brain damage, neurological disease, drug/alcohol misuse during the past year, other severe psychiatric or somatic disorders, orthostatic hypertension or hypersensitivity to test preparation. Wash out periods for psychotropic drugs (except benzodiazepines) MAOIs, and fluoxetine of at least 1,2 and 5 weeks respectively. All psychotropic drugs except oxazepam were proscribed.	70% female All Caucasian Mean age 38 years no difference between groups		<u>Efficacy</u> Primary measure was number of responding patients at week 8 for the ITT population and by use of 'last observation carried forward'. Measures # panic attacks using panic attack item of Clinical Anxiety Scale (CAS) Physician's and Patient's self assessment using the Global Improvement Scale (OYGIS and PATGIS respectively). Hamilton Anxiety Rating Scale (HARS) MADRS <u>Safety and Tolerability</u>
Results: treatment, comparator data, dropouts (numbers/percentage and reasons), treatment emergent adverse events (whether spontaneous report or questioned by researcher/treating clinician), investigator's conclusions and reviewers conclusions if different from investigators								
36 patients reported adverse events which caused or contributed to withdrawal.								
Citalopram appears to be more efficacious than placebo, with in the 20-30 mg group more effective than the higher does group.								
There was a large increase in placebo response week 4-6.								

Table 2 MADRS and HAS scores at baseline and final assessment (LOCF)

	Placebo	Citalopram			Clomipramine
	(n=96)	10-15 mg (n=97))	20-30 mg (n=95)	40-60 mg (n=98)	60-90 mg (n=98)
HAS total	23.0	23.5	22.9	23.0	24.2
Baseline	15.6	13.6**	12.3***	1.4***	12.7***
Last assessment					
HAS psychic	12.6	12.6	12.0	12.7	13.2
Baseline	8.8	7.4*	6.3***	6.0***	6.7***
Last assessment					
HAS somatic	10.4	10.9	10.9	10.3	11.0
Baseline	6.8	6.2	6.0*	5.4**	6.0**
Last assessment					
MADRS	11.9	12.0	11.4	11.6	12.9
Baseline	9.5	8.2	6.5***	6.5***	6.9***
Last assessment					

*P<0.1. **P<0.05. ***P<0.01.

Table 3 Number and percentage of treatment-emergent adverse events

Adverse event	Placebo		Citalopram		Clomipramine
	n(%)	10-15 mg n (%) ¹	20-30 mg n (%)	40-60 mg n(%) ¹	60-90mg n(%) ²
Headache	27 (28)	32 (33) ¹	25 (26)	26 (29) ¹	16 (16)
Nausea	17 (18)	26 (27)	27 (28)	26 (29)	29 (30)
Mouth dry	14 (15)	12 (12) ¹	11 (12) ¹	15 (17) ¹	32 (33) ²
Increased sweating	7 (7)	10 (10)	17 (18) ²	14 (16)	19 (19) ²
Dizziness	6 (6)	9 (9)	13 (14)	6 (7) ¹	18 (18) ²
Insomnia	7 (7)	8 (8)	10 (11)	6 (7)	16 (16)
Abdominal pain	5 (5)	4 (4)	5 (5) ¹	6 (7) ¹	0 (0) ²
Tremor	5 (5)	3 (3) ¹	7(7)	2 (2)	17 (17) ₂
Constipation	2 (2)	1 (1)	3 (3)	2 (2)	7 (7)
Anorgasmia	0 (0)	1 (2)	6 (9) ²	7 (10) ²	6 (10) ²

¹ Significantly different from clomipramine.

² Significantly different from placebo.

RCT extraction table

Author (s)	Study (placebo controlled, active comparator etc.)	Type of intervention (pharmacotherapy & name of therapy) Length of study	Setting and location (primary/secondary care or other & country)	Numbers randomised Randomisation method Numbers incl in results analysis (Confirm ITT analysis or % included in results)	Inclusion criteria/ Exclusion criteria Exclusion of depression Permitted polycharmacy Washout period Substance misuse Concordance (compliance)	Mean age (years) Male/female (M/F) ratio Ethnicity	Follow-up period	Main outcome measures (extract data on primary outcome measure only and just note secondary outcome)
Leploa, Wade, Leinonen, Koponen	Variable dose Citalopram 10-15mg/day Citalopram 20-30mg/day Citalopram 40-60mg/day placebo controlled active comparator clomipramine 60-90mg/day	Citalopram long-term study clomipramine 8 week short-term study 1 year long-term study	Setting: Out-patients Location 4 countries 22 centres	Numbers: 8 week short-term study: 475 1 year long-term study: 279 randomisation: ? concealment of allocation: ? baseline comparability: ? numbers in results: ITT: 258 Completers: 161 Largely similar results. ITT quoted	Inclusion: Age 18-65 Diagnosed panic disorder +/- agoraphobia (DSM-III-R) Exclusion: Severe depressive symptoms (>22 on Montgomery –Asberg depression scale) Organic brain disease Neurological disease Drug/alcohol abuse <1 year Severe psychiatric/somatic disorders Orthostatic hypotension Hypersensitivity Pregnancy/intention thereof Polypharmacy: Concurrent psychotropic drugs not allowed	Age: Mean 39, range 18-61 years Gender: 143 men: 332 women Ethnicity ?	Follow-up : 1 year assessments at: 8 weeks, 3,6,8,12 months	Primary: No panic attack in 1 week prior to assessment as defined by only scores of 0 or 1 on CAS (Clinical Anxiety Scale). Percentages at 8 weeks, 3,6,9months (estimated from graph) Citalopram 10-15mg/day: 52,56,64,66% Citalopram 20-30mg/day 67, 74,78,79% Citalopram 40-60mg/day 63,70,76,75% clomipramine 60-90mg/day 55,60,62,63% placebo 46,48,49,50% comparison to placebo at ?12months Citalopram 20-30mg/day p=0.001 Citalopram 40-60mg/day p=0.003 secondary: retention of patients Physician's Global Improvement Scale Patient's Global Improvement Scale
Results: treatment, comparator data, dropouts (numbers/percentage and reasons), treatment emergent adverse events (whether spontaneous report or questioned by researcher/treating clinician), investigator's conclusions and reviewers conclusions if different from investigators)								

Dropouts:

Citalopram 10-15mg/day: 24(43%)
Citalopram 20-30mg/day: 14 (22%)
Citalopram 40-60mg/day: 18(31%)
clomipramine 60-90mg/day: 26 (43%)
placebo 18 (44%)

reasons: those dropping out due to ineffectiveness was slightly higher in the placebo group than the intervention groups.

treatment emergent adverse events:

observed/spontaneous patient report/ response to open question

vital signs and labs

discontinuation due to AEs:

Citalopram 10-15mg/day: 4

Citalopram 20-30mg/day: 3

Citalopram 40-60mg/day: 1

clomipramine 60-90mg/day: 4

placebo: 1

all patients in study reported at least one adverse event. No clustering of emergent AEs. Headache lower in clomipramine than citalopram or placebo

investigators conclusions: citalopram in the dose range of 20-60mg/day is effective, well-tolerated and safe in the long-term treatment of patients who have panic disorder

reviewers comments:STUDY DESIGN

objectives of trial sufficiently described: yes

satisfactory statement of *diagnostic criteria* for trial: yes

satisfactory statement of *source of patients*:no

method of randomisation :?

concealment of allocation:?

blinding:?

delay between allocation and commencing intervention: ?

outcome measures: stated, appropriate, *validity* thereof: outcome measure very arbitrary and of questionable validity.

sample size calculation : not shown

post-intervention follow-up: none

STUDY CONDUCT

comparability of groups re baseline characteristics: not shown

losses to follow-up: small (but not completely clear)

numbers of *non-completers* of intervention: large

description of non-completers: none. Not described of those who chose not to continue after 8 weeks

adverse effects: data not explicit

ANALYSIS AND PRESENTATION**reviewers conclusions:**

level of evidence:

Not completely clear re numbers, whether ITT analysis

Primary outcome: numbers and percentages not shown, confidence intervals not shown

Degree of modelling and adjustment not clear

reviewers conclusions:

citalopram in the dose range of 20-60mg/day is effective, well-tolerated and safe in the long-term treatment of patients who have panic disorder, reducing panic attacks in 79% compared to 50% in the placebo group

substantial improvement in placebo group ie relatively small treatment effect

large drop-out rate

much potential for bias

level of evidence:

1-

RCT extraction table

Author (s)	Study (placebo controlled, active comparator etc.)	Type of intervention (pharmacotherapy & name of therapy) Length of study	Setting and location (primary/secondary care or other & country)	Numbers randomised Randomisation method Numbers incl in results analysis (Confirm ITT analysis or % included in results)	Inclusion criteria/ Exclusion criteria Exclusion of depression Permitted polycharmacy Washout period Substance misuse Concordance (compliance)	Mean age (years) Male/female (M/F) ratio Ethnicity	Follow-up period	Main outcome measures (extract data on primary outcome measure only and just note secondary outcome)
Stahl, S. M. et al (2003) Escitalopram in the treatment of panic disorder: a randomized, double-blind, placebo controlled trial Journal of Clinical Psychiatry, 64: 1322-27	Randomized, double-blind, parallel group, flexible-dose, placebo-controlled, multicenter study	Single blind, 2-week placebo lead in preceded 10 week double-blind treatment phase See Table A overleaf Overall mean daily dose: Escitalopram 10.8mg Citalopram 21.3mg Patients seen at study entry, day of randomization and at end of weeks 1, 2, 4, 6, 8, 10	Outpatients other details not given	Safety analyses – 366 patients Placebo 119, escitalopram 128, citalopram 119 Efficacy analyses (ITT subset) 351 Placebo 114, escitalopram 125, citalopram 112 68% of all randomized patients completed study (60.5% placebo, 75.8% escitalopram, 68.1% citalopram) Reasons for discontinuation Lost to follow-up 10.7% Adverse events 7.4% Insufficient therapeutic response 5.7% Withdrawal of consent 4.4% Protocol violation 3.0% Other 0.5% Intention to treat analysis (i.e. all who received at least 1 dose of double blind study medication, at least 1 post baseline panic attack, using last-observation carried forward).	Inclusion: male and female outpatients, aged 18-80, DSM-IV panic disorder with or without agoraphobia, minimum 4 panic attacks (DSM-IV defined) – at least 1 was anticipated, during 4 weeks prior to screening visit and at least 3 attacks during the 2 week placebo lead-in period. Exclusion: score >17 on Hamilton Rating Scale for depression, bipolar disorder, other psychotic disorder, psychoactive substance use disorder within past 6 months, pregnancy, clinically significant abnormalities in laboratory evaluations or ECG readings patients who had received treatment with neuroleptic, antidepressant or anxiolytic medication within 2 weeks prior to study entry. Patients receiving regular daily therapy with any benzodiazepines within 1 month prior to first administration of study medication. Polypharmacy: subjects not allowed to take any psychotropic medication except zolpidem as needed for sleep.	Placebo: mean age 38.6 years; %age female 55.3; ethnicity % white 71.1 Escitalopram: mean age 37.5 years; %age female 57.6; ethnicity % white 70.4 Citalopram: mean age 37.1 years; %age female 61.6; ethnicity % white 75.9	Study period 10 weeks in total	Primary: panic attack frequency at week 10. Secondary: panic and agoraphobia scale (P&A); Clinical Global Impressions – Improvement Scale (CGI-I); Severity of Illness Scale (CGI-S); Hamilton Rating Scale for Anxiety (HAM-A); Patient Global Evaluation (PGE); Anticipatory Anxiety Duration; Quality of Life Enjoyment and Satisfaction Questionnaire (Q-LES-Q)
Results: treatment, comparator data, dropouts (numbers/percentage and reasons), treatment emergent adverse events (whether spontaneous report or questioned by researcher/treating clinician), investigator's conclusions and reviewers conclusions if different from investigators)								

Table A

	Begin	End of week 1	Could be increased at end of week 4
Placebo	1 tablet/day	2 tablets/day	matching
Escitalopram	5mg/day	10mg/day	20mg/day
Citalopram	10mg/day	20mg/day	40mg/day

Table 2. Efficacy Results at Endpoint^a

Variable	Placebo (N=114)	Escitalopram (N=125)	Citalopram (N=112)
Panic attack frequency, ^b log (endpoint/baseline)	-1.32 ± 0.1	-1.61 ± 0.1*	-1.43 ± 0.1
Zero panic attacks, %	38	50□	39
P&A Scale total score	-3.9 ± 0.9	-8.9 ± 0.9**	-7.4 ± 0.8**
Anticipatory anxiety duration, % of time	-11.7	-24.3	-22.1
HAM-A score	-4.6 ± 0.8	-6.1 ± 0.7**	-4.9 ± 0.7
CGI-I score	2.8 ± 0.1	2.2 ± 0.1**	2.2 ± 0.1**
CGI-Phobic Avoidance score	3.1 ± 0.1	2.5 ± 0.1**	2.6 ± 0.1**
CGI-S score	-1.2 ± 0.1	-1.6 ± 0.1**	-1.5 ± 0.1*
PGE score	2.8 ± 0.1	2.3 ± 0.1**	2.2 ± 0.1**
Q-LES-Q score	2.8 ± 1.1	7.2 ± 1.1**	5.8 ± 1.0*

^aValues represent changes from baseline except for zero panic attacks and CGI-I, CGI-Phobic Avoidance, and PGE scores, for which values are those at endpoint. Values shown as mean ± SEM.

^bPrimary efficacy measure.

*p ≤ .05 vs. placebo.

**p < .01 vs. placebo.

Abbreviations: CGI-I = Clinical Global Impressions-Improvement scale, CGI-S = CGI-Severity of Illness scale, HAM-A = Hamilton Rating Scale for Anxiety, P&A = Panic and Agoraphobia, PGE = Patient Global Evaluation, Q-LES-Q = Quality of Life Enjoyment and Satisfaction Questionnaire.

Authors conclusions

Discontinuation due to adverse events for escitalopram was 6.3% compared with 7.6% for placebo, 8.4% for citalopram. The most common adverse event was similar for escitalopram and placebo. Therefore, escitalopram is safe, well tolerated and effective.

Other results

No statistical separation of citalopram treatment from placebo treatment in terms of relative panic attack frequency.

Note

Study supported by Forest Laboratories Inc. Lead author received grant/research support and been a consultant/received honoraria from numerous pharmaceutical companies. Other 2 authors are employees of Forest Laboratories.

Benzodiazepine (diazepam)/beta blocker (propranolol)

RCT extraction table

Author (s)	Study (placebo controlled, active comparator etc.)	Type of intervention (pharmacotherapy & name of therapy) Length of study	Setting and location (primary/sec ondary care or other & country)	Numbers randomised Randomisation method Numbers incl in results analysis (Confirm ITT analysis or % included in results)	Inclusion criteria/ Exclusion criteria Exclusion of depression Permitted polypharmacy Washout period Substance misuse Concordance (compliance)	Mean age (years) Male/female (M/F) ratio Ethnicity	Follow-up period	Main outcome measures (extract data on primary outcome measure only and just note secondary outcome)
Noyes R, Jr., Anderson DJ, Clancy J, Crowe RR, Slymen DJ, Ghoneim MM et al. Diazepam and propranolol in panic disorder and agoraphobia. Archives of General Psychiatry 1984;41:287-92.	Active comparator	Pharmacotherapy Diazepam 15mg/day vs Propranolol 15mg/day 2 weeks one drug and following a cross-over design – two weeks another drug	US – Iowa University Hospital patients	27 randomised Randomisation method not stated Numbers included = 21 patients 78% included in results analysis 6 dropped out 1 st 2 weeks of therapy: 4 PROPRANOLOL 1 DIAZEPAM 2 (not stated)	Included if: met DSM-III criteria for agoraphobia, panic disorder, or generalised anxiety disorder and reported at least moderately severe symptoms at initial evaluation. Included patients had a median Hamilton Anxiety Scale score of 25 Excluded if: presence of physical disorders that might account for anxiety symptoms, suffering from diabetes, asthma or heart disease or pregnant.	Mean age 34.8 years (range 20 to 61 years). Male/Female ratio: 8/13. No information on ethnicity	1 week for four patients who wished to continue on a combination of propranolol and diazepam	Symptom Checklist –90 (SCL-90) HAM-A Resting heartrate and blood pressure 5 point rating scale for side-effects Plasma drug levels
Results: treatment, comparator data, dropouts (numbers/percentage and reasons), treatment emergent adverse events (whether spontaneous report or questioned by researcher/treating clinician), investigator's conclusions and reviewers conclusions if different from investigators								

Dosage: 5mg DZ: 40mg propranolol hydrochloride. Patients were assigned to either sequence 1: 4 day titration on diazepam and maintenance until day 14 and then stop diazepam and titrated for 4 days to propranolol or vice versa for sequence 2.

The response to diazepam was shown to be significantly superior to the response to propranolol on all self- and observer-rating scales. Propranolol had no influence on the numbers of attacks

Refer to tables 2, 3 & 4 per the paper above

Comparison of symptom reduction by each drug was made for a two-period, repeated measurements, crossover design using a multivariate (over time) ANOVA.

Observer-rated improvement during second week of drug administration

Improvement	Diazepam N=21	Propranolol N=21
None	1	11
Slight	2	3
Moderate	4	5
Marked	11	2
Complete	3	0

Conclusions: Panic attacks and phobic symptoms responded to diazepam, but not to propranolol. The results suggest that benzodiazepines constitute effective short-term treatment for these newly defined disorders.

Table 2 – Multivariate Analysis of Variance on Anxiety Scale Scores during Drug Administration*

	<i>Carryover</i>		<i>Drug</i>		<i>Period</i>		<i>Week</i>		<i>Drug x Week</i>	
	<i>F</i>	<i>P</i>	<i>F</i>	<i>P</i>	<i>F</i>	<i>P</i>	<i>F</i>	<i>P</i>	<i>F</i>	<i>P</i>
SCL-90 [†] anxiety scale	0.01	NS	10.1	.005	0.19	NS	0.28	NS	2.67	NS
SCL-90 somatic scale	0.35	NS	8.0	.01	0.07	NS	0.02	NS	0.89	NS
Hamilton Anxiety Scale	0.72	NS	20.1	<.001	0.90	NS	0.01	NS	0.12	NS
Global severity scale	0.39	NS	38.6	<.001	0.14	NS	0.01	NS	0.25	NS
Global relief scale	0.53	NS	25.3	<.001	2.81	NS	0.02	NS	0.03	NS
Heart rate	0.27	NS	71.5	<.001	2.48	NS	0.01	NS	2.69	NS
Systolic BP	9.00	.009	2.96	NS	0.30	NS
Diastolic BP	4.12	.06	2.31	NS	0.45	NS

*Degrees of freedom were 1 and 19 for each test. Carryover x week and period x week interaction were also examined: with one exception, noted in the text, these were not found statistically significant. Only *P* values less than .10 are shown.

[†]SCL-90 indicates Symptom Checklist-90.

Table 3 – Mean (\pm SD) Anxiety Scale Scores During Drug Administration

	Sequence*	N	Baseline	Period 1		Period 2	
				Week 1	Week2	Week 1	Week 2
SCL-90 \ddagger anxiety scale	D-P	12	17.2 \pm 12.3	9.2 \pm 9.7	6.2 \pm 5.5	13.5 \pm 8.6	14.8 \pm 6.3
	P-D	9	19.7 \pm 10.5	12.2 \pm 10.2	14.6 \pm 9.1	7.6 \pm 6.6	9.3 \pm 9.4
SCL-90 somatic scale	D-P	12	21.2 \pm 8.9	9.6 \pm 10.5	5.6 \pm 7.0	12.3 \pm 8.2	12.1 \pm 5.9
	P-D	9	15.4 \pm 6.5	13.8 \pm 10.8	15.3 \pm 11.1	8.1 \pm 7.6	10.0 \pm 10.5
Hamilton Anxiety scale	D-P	12	25.6 \pm 10.7	12.4 \pm 7.9	9.6 \pm 8.3	20.6 \pm 10.5	19.8 \pm 7.6
	P-D	9	26.9 \pm 5.5	20.8 \pm 7.0	22.0 \pm 11.0	14.3 \pm 9.1	16.4 \pm 11.7
Global severity scale	D-P	12	3.08 \pm 0.79	1.58 \pm 0.79	1.50 \pm 0.80	2.67 \pm 0.89	2.58 \pm 0.79
	P-D	9	3.11 \pm 0.33	2.89 \pm 0.93	2.89 \pm 0.93	1.56 \pm 0.88	1.78 \pm 1.30
Global relief scale	D-P	12	...	2.33 \pm 0.78	2.67 \pm 0.49	0.75 \pm 0.87	0.92 \pm 0.79
	P-D	9	...	1.56 \pm 1.01	1.33 \pm 1.00	2.44 \pm 1.01	2.11 \pm 1.05
Heart rate	D-P	11	79.7 \pm 21.1	81.0 \pm 12.6	76.8 \pm 13.2	59.5 \pm 8.3	60.8 \pm 7.9
	P-D	8	72.1 \pm 11.6	59.4 \pm 6.8	63.0 \pm 7.9	74.4 \pm 10.4	73.8 \pm 10.8
Systolic BP	D-P	9	128.3 \pm 13.9	...	125.6 \pm 7.3	...	121.1 \pm 12.9
	P-D	7	121.3 \pm 12.0	...	105.0 \pm 16.1	...	113.6 \pm 10.7
Diastolic BP	D-P	9	87.5 \pm 8.6	...	85.6 \pm 6.3	...	80.0 \pm 11.5
	P-D	7	81.3 \pm 9.8	...	73.6 \pm 10.3	...	75.7 \pm 8.9

*D indicates diazepam; P, propranolol hydrochloride. \ddagger SCL-90 indicates Symptom Checklist-90.

Table 4 - Mean (\pm SE) Number and severity of Panic Attacks and Severity of Phobic Symptoms and Social Impairment During Drug Therapy

	<i>Baseline</i>	<i>Propranolol</i>		<i>Diazepam</i>	
		<i>Week 1</i>	<i>Week 2</i>	<i>Week 1</i>	<i>Week 2</i>
Panic attacks (N = 17) No.	8.5 + 2.279	8.2 + 1.82	6.4 + 1.26	2.2 + 0.53	2.9 + 0.84
Severity	2.2 + 0.20	1.9 + 0.19	2.0 + 0.19	1.4 + 0.28	1.2 + 0.26
Phobic symptoms (N = 19) Severity	2.2 + 0.21	1.5 + 0.26	1.6 + 0.27	0.7 + 0.17	1.0 + 0.19
Social impairment (N = 21) Severity	2.2 + 0.18	1.9 + 0.19	1.9 + 0.18	0.9 + 0.22	1.0 + 0.26

SSRIs

Paroxetine

Author (s)	Research question	Review type Databases used Time period covered Data analysis	Study design Interventions Follow-up period	Numbers randomised Randomisation method Numbers incl in results analysis	Total sample number Age (mean/SD/range) Male/female Ethnicity	Outcomes
30. Lecrubier Y, Bakker A, Dunbar G, Judge R. 1997 A comparison of paroxetine, clomipramine and placebo in the treatment of panic disorder. Collaborative Paroxetine Panic Study Investigators.	The aim was to compare paroxetine with clomipramine .		12-week, double-blind, parallel group, placebo-controlled study		367 patients with DSM-III-R defined panic disorder	Efficacy assessments included the daily panic attack diary, the Clinical Global Impression Scale, the Hamilton Anxiety Rating Scale, the Marks Sheehan Phobia Scale and the Sheehan Disability Scale.
<p style="text-align: center;">Results: treatment, comparator data, dropouts (numbers/percentage and reasons), treatment emergent adverse events (whether spontaneous report or questioned by researcher/treating clinician), investigator's conclusions and reviewers conclusions if different from investigators</p> <p>More patients in the paroxetine group had no panic attacks at the end of 12 weeks. Paroxetine had a slightly earlier onset compared to clomipramine</p>						

Paroxetine – long term evaluation

Author (s)	Research question	Review type Databases used Time period covered Data analysis	Study design Interventions Follow-up period	Numbers randomised Randomisation method Numbers incl in results analysis (Confirm ITT analysis or % included in results)	Total sample number Age (mean/SD/range) Male/female Ethnicity	Outcomes
31. Lecrubier Y, Judge R. 1997 Long-term evaluation of paroxetine, clomipramine and placebo in panic disorder. Collaborative Paroxetine Panic Study Investigators.	This trial studied the longer term effects of paroxetine		Patients who satisfactorily completed a 12-week, double-blind, placebo-controlled study of paroxetine and clomipramine could choose to continue receiving their randomized treatment for a further 36 weeks	In total, 176 patients were included in the intention-to-treat population.	Patients with DSM-III-R defined panic disorder.	Efficacy assessments included the daily panic attack diary, the Clinical Global Impression Scale, the Hamilton Anxiety Rating Scale, the Marks Sheehan Phobia Scale and the Sheehan Disability Scale
<p align="center">Results: treatment, comparator data, dropouts (numbers/percentage and reasons), treatment emergent adverse events (whether spontaneous report or questioned by researcher/treating clinician), investigator's conclusions and reviewers conclusions if different from investigators</p> <p>Panic attacks in the active treatment groups continued to decrease during maintenance study. At the end of the continuation period (12+36=48 weeks) % of subjects free from panic attacks were</p> <p>85% Paroxetine 72% Clomipramine 59% Placebo</p>						

Benzodiazepines

Clonazepam/placebo

RCT extraction table

Author (s)	Study (placebo controlled, active comparator etc.)	Type of intervention (pharmacotherapy & name of therapy) Length of study	Setting and location (primary/secondary care or other & country)	Numbers randomised Randomisation method Numbers incl in results analysis (Confirm ITT analysis or % included in results)	Inclusion criteria/ Exclusion criteria Exclusion of depression Permitted polycharmacy Washout period Substance misuse Concordance (compliance)	Mean age (years) Male/female (M/F) ratio Ethnicity	Follow-up period	Main outcome measures (extract data on primary outcome measure only and just note secondary outcome)
Valenca AM, Nardi AE, Nascimento I, Mezzasalma MA, Lopes FL, Zin W. Double-blind clonazepam vs placebo in panic disorder treatment. Arquivos de Neuro-Psiquiatria 2000;58:1025-9. ○	Placebo controlled	Pharmacotherapy: Clonazepam vs placebo 6 weeks	Laboratory of Panic & respiration, Uni. Of Rio de Janeiro	24 randomised Randomisation method not stated 22 included in the results analysis 92% included in results analysis	Included if: aged between 18 & 55, at least 3 panic attacks in the last two consecutive weeks before the first challenge test day, were healthy enough to participate according to physical exam and lab test, free of psychotropic drugs at least one week and no BDZs or other meds. Excluded if: comorbid mental disorder, history of psychosis, bipolar disorder, epilepsy, pregnancy, substance abuse within 6 months of participation, any comorbid major medical disorder	Mean age 37 years, SD 6.9 years M/F ratio: Clonazepam group: 5M/9F PL group: 5/5 Ethnicity not specified other than patients who were attendees or a Brazilian hospital	Not stated	Change in number of panic attacks from baseline Clinical Global Impression - CGI (of panic disorder, phobic avoidance, anticipatory anxiety) Patient Global Impression – PGI Reduction of ≥ 50% in HAM-A and the Panic Associated Symptom Scale

Results: treatment, comparator data, dropouts (numbers/percentage and reasons), treatment emergent adverse events (whether spontaneous report or questioned by researcher/treating clinician), investigator's conclusions and reviewers conclusions if different from investigators

Dosage: 2mg/day

Placebo group (n=9)	Clonazepam group (n=13)			
	Baseline	Endpoint	Baseline	Endpoint
Status panic free		11.1%		61.5% (Fisher exact test p=0.031)
CGI	4.7 +/- 0.8	3.5+/-1.2	4.4 +/-0.7	1.5 +/-0.8 (Tukey test, df= 1, p<0.05)
PGI		3.1 +/-1.66		2 +/-0.87 (T test, p=0.108)
Intensity of anticipatory anxiety		Anticipatory anxiety (mean %)	51 +/-27.6	40.5 +/- 25.5 55 +/- 32.9 14.7 +/- 7.6 (T test, p=0.037)
Score of phobias	7.7 +/- 1.9	6 +/- 2.3	8 +/- 1.8	3 +/- 2.6 (T test, p=0.034)
50% reduction in Hamilton score	7 +/- 3.5	5.8 +/- 2.7	8.4 +/- 1.5	3.5 +/- 2.6 (T test, p<0.001)
		33.3%		76.9% (Fisher exact test, p=0.079)
Adverse events	n	%	n	%
Somnolence			7	53.8
Ataxia			4	30.8
Memory Problems	1	11.1	2	15.4
Dizziness	2	22.2	3	23
Irritability			1	7.6
Depression			1	7.6
Libido decrease			1	7.6
None	6	66.6	2	15.4

Investigator conclusions: there is evidence for the efficacy of clonazepam in panic disorder patients.

Reviewers comments: Significantly more patients are panic free when treated with clonazepam compared to placebo and experienced a significantly greater reduction in anxiety as measured by the HAM-A. The trial does not report the intensity of adverse events experienced by patients. Trial participant numbers are very small. Although clinicians reported accorded a greater improvement in symptoms, patients perceptions did not reflect this trend.

Impact of benzodiazepines on psychological therapy

RCT extraction table

Author (s)	Study (placebo controlled, active comparator etc.)	Type of intervention (pharmacotherapy & name of therapy) Length of study	Setting and location (primary/sec ondary care or other & country)	Numbers randomised Randomisation method Numbers incl in results analysis (Confirm ITT analysis or % included in results)	Inclusion criteria/ Exclusion criteria Exclusion of depression Permitted polycharmacy Washout period Substance misuse Concordance (compliance)	Mean age (years) Male/female (M/F) ratio Ethnicity	Follow-up period	Main outcome measures (extract data on primary outcome measure only and just note secondary outcome)
van Balkom AJLM, de Beurs E, Koele P, Lange A, van Dyck R. Long-term benzodiazepine use is associated with smaller treatment gain in panic disorder with agoraphobia. Journal of Nervous and Mental Disease 1996;184:133-5.	Active comparator: Fluvoxamine with exposure in vivo; Placebo with exposure in vivo; psychological panic management with exposure in vivo; exposure in vivo alone	Psychological therapy as affected by level, if any, of benzodiazepine use	Outpatient clinical for anxiety disorders of the psychiatric center Amsterdam.	96 patients randomised Randomisation method not stated 76 or 79% included in results analysis. No ITT analysis	Included if: between 18 & 65 years, met DSM-III-R criteria for panic disorder with moderate/severe agoraphobia with a duration of at least 6 months. Patients selected on severod of agoraphobic avoidance; no minimal frequency of panic attacks required. Excluded if: Depressed, psychotic, organic or mental disorders, psychoactive substance use, pregnant, lactating, unwilling to stop neuroleptic or antidepressant drugs. Concomitant use of BDZs permitted if the patients had been taking them for more than 3 months and were willing to keep the use at a constant level during trial.	Refer to de Beurs et al 1995 {994}	None stated	Agoraphobic subscale of the Fear Questionnaire, the Symptoms checklist 90 and the Mobility Inventory avoidance alone scale Number of panic attacks recorded in a diary for weekly panic frequency

Results: treatment, comparator data, dropouts (numbers/percentage and reasons), treatment emergent adverse events (whether spontaneous report or questioned by researcher/treating clinician), investigator's conclusions and reviewers conclusions if different from investigators

Fluvoxamine dose = 150mg/day for all groups

The influence of benzodiazepine use on the residual gain score (multiple regression analysis with the residual gain score as dependent variable. The residual gain score corrects for the influence of the pretest level on the raw change score).

The influence on treatment condition on outcome:

Treatment condition significantly predicted treatment gain: $R=0.55$; $f[3]=24.00$; $p<.0001$ in 22% of cases whether or not patient were treated with fluvoxamine plus exposure in vivo ($\beta = -.46$; $t=-4.68$; $p<0.0001$)

Both treatment condition and use of BDZs significantly affected treatment outcome but not interaction was found between treatment and long-term BDZ use ($F [3,68]=.19$; $p=.90$)

To test whether long-term use of BDZ is a reflection of more severe psychopathology, both groups of patients were compared using t-tests on panic frequency in first treatment week and pretest scores on the composite scale of agoraphobia. Significant differences were found for frequency of panic attacks ($t[1]=4.47$; $p=.04$) and depression ($t[1] = 7.71$; $p=.007$). Long-term BDZ users reported fewer panic attacks (mean = 0.9 +/-SD 0.9) and more severe depression (5.1 +/-1.6) compared with incidental or nonusers (respectively: 2.0 +/-2.2; depression: 4.2 +/-1.2)

There were no differences on the severity of agoraphobic avoidance.

Conclusion: Long-term benzodiazepine use was associated with less treatment gain compared with incidental or non-use in all four treatment conditions. Long-term use of BDZs accounted for 7% of the variance in residual treatment gain. The authors state that this must be interpreted as a 'medium' effect according to Cohen 1988 {10946}. This however, does not mean it is a equivalent to a clinically unimportant effect.

Cohort Study

Author (s)	Study Design	Comparisons	Setting and location	Numbers of participants	Inclusion criteria/ Exclusion criteria	Characteristics of participants	Follow-up period	Main outcome measures Analysis
Westra, H. A., Stewart, S. H., & Conrad, B. E. 2002, "Naturalistic manner of benzodiazepine use and cognitive behavioral therapy outcome in panic disorder with agoraphobia", <i>Journal of Anxiety Disorders</i> , vol. 16, no. 3, pp. 233-246.	<p>Naturalistic study of BZ use with CBT in patients with PD with agoraphobia.</p> <p>The authors hypothesis is that pattern of use of BZ may be an important mediator of CBT outcome.</p> <p>All patients received 10 sessions of group CBT</p> <p>This study observed prn users</p>	<p>Before and after</p> <p>Different usage of BZ</p> <p>No placebo or comparators.</p>	Canada	43	<p>Inclusion</p> <ul style="list-style-type: none"> Met DSM-IV criteria for PDA assessed via interview with lead author. 	<p>31 Females</p> <p>33 were taking BZ – 11 of these were also taking antidepressants and 1 a betablocker</p> <p>10 were unmedicated</p>	None	<p>Beck Anxiety Inventory</p> <p>Panic Attach Questionnaire Revised.</p> <p>BZ use – type, dose, chonicity and frequency</p> <p>To assess predictors of change in symptom status as a function of treatment a series of 5 regressions were conducted.</p>

Results

Subjects improved significantly on all measures of treatment from pre-post treatment.
 As a group prn BZ users demonstrated a significantly poorer CBT response compared to non-medicated subjects.
 A lot of confounders in this study
 Conclusion – manner of BZ use may be an important variable in CBT outcome

Tricyclics

Imipramine

Meta analysis/systematic review extraction table

Author (s)	Research question	Review type Databases used Time period covered Data analysis	Study design Interventions Follow-up period	Numbers randomised Randomisation method Numbers incl in results analysis (Confirm ITT analysis or % included in results)	Total sample number Age (mean/SD/range) Male/female Ethnicity	Outcomes
Cox et al A meta-analysis of treatment for panic disorder with agoraphobia: imipramine, alprazolam, and in vivo exposure 1992 J. Behav. Ther. & Exp. Psychiat.	To assess differences in dependent variables (including symptoms of PD such as panic attack severity, dysphoria, avoidance behaviour) response to treatment with imipramine, alprazolam and in vivo exposure. For this extraction, focus will be on the effect sizes calculated for imipramine only.	Type: Systematic review Databases: Psychlit, medline Time period: 1980-90 Data analysis: calculation of effect sizes using Cohens d; conversion to Z-scores; comparisons made between Z scores	RCTs Imipramine Alprazolam In vivo exposure Follow-up: none	Numbers randomised: not stated Randomisation method: not given Not confirmed whether studies used ITT analysis	34 studies included Sample number, age, male/female ratio and ethnicity not given	(as listed in review) 1. Dysphoria or depression 2. Frequency of panic attacks per week (based on self-report) 3. Severity of panic attacks (based on self-report ratings) 4. Agoraphobic fear 5. Agoraphobic avoidance behaviour 6. Generalized anxiety 7. Overall improvement ratings (clinician-rated) Pre and post-treatment values used
Results: treatment, comparator data, dropouts (numbers/percentage and reasons), treatment emergent adverse events (whether spontaneous report or questioned by researcher/treating clinician), investigator's conclusions and reviewers conclusions if different from investigators						
<p>Dosage Mean for Imipramine: 158.8 mg/day (range = 95.2 – 300). The review records that the highest number of dropouts of each of the three treatments was in the imipramine group at 28.5% (range = 16.7-42.3%) It is pointed out that the averaged effect sizes reported in Table 1 may give a more accurate portrayal of treatment efficacy than do the Z-scores because the significance of the Z-scores is dependent on the number of studies used.</p>						
From this meta-analysis, the author's conclude that imipramine was found to be generally ineffective						

Specific Treatment Effects of Alprazolam, Imipramine, and Exposure for PDA

Treatment variable	n	Effect size	Z
Alprazolam			
Global severity (clinician rated)	9	2.10	2.17†
Anxiety	12	1.53	2.10†
Depression	6	0.81	0.93
Panic frequency	7	1.34	1.48*
Panic severity	4	1.76	1.32*
Agoraphobic fear	7	1.21	1.37*
Total fears	0	-	-
Behavioral fear test	0	-	-
Imipramine			
Global severity (clinician rated)	7	1.16	1.33*
Anxiety	9	1.62	1.89†
Depression	6	1.53	1.48*
Panic frequency	6	0.97	1.07
Panic severity	2	1.60	0.90
Agoraphobic fear	5	0.91	0.93
Total fears	3	0.86	0.68
Behavioral fear test	1	1.59	0.62
Exposure			
Global severity (clinician rated)	5	3.42	1.93†
Anxiety	4	2.28	1.50*
Depression	6	1.46	1.44*
Panic frequency	4	1.34	1.11
Panic severity	2	2.20	1.04
Agoraphobic fear	9	3.32	2.57‡
Total fears	7	2.00	1.87†
Behavioral fear test	9	1.83	2.03†

*p < 0.10; †p < 0.05; ‡p < 0.01.

Meta analysis/systematic review extraction table

Author (s)	Research question	Review type Databases used Time period covered Data analysis	Study design Interventions Follow-up period	Numbers randomised Randomisation method Numbers incl in results analysis (Confirm ITT analysis or % included in results)	Total sample number Age (mean/SD/range) Male/female Ethnicity	Outcomes																													
Mattick, Andrews, Hadzi-Pavlovic & Christensen Treatment of Panic and Agoraphobia – an integrative review	Exploration of symptom improvement in response to both pharmacological and psychological treatments	Systematic review Databases: PsycInfo, Medline and ERIC, bibliographies of review articles. Imipramine (alone) studies, i.e. not combined with behavioural or other pharmacological treatment 1978-1985	RCT Interventions: all. Focus on analysis of imipramine for PD Follow-up: no follow-up of 4 studies mentioned	Numbers randomised: not given but average sample size = 46 patients	Mean sample size = 46 patients Mean age of patients = 37 years Mean duration of illness = 9 years Male/female ratio= 1: 4.7	Phobia measures (unspecified): self-ratings, observer ratings, established inventories and behavioural avoidance tests Panic measures (unspecified): frequency, intensity, duration, or global ratings Anxiety measures (unspecified): e.g. HAM-A Depression measures (unspecified): outside scope																													
Results: treatment, comparator data, dropouts (numbers/percentage and reasons), treatment emergent adverse events (whether spontaneous report or questioned by researcher/treating clinician), investigator’s conclusions and reviewers conclusions if different from investigators																																			
<p>Included studies (Evans et al. 1986), (Mavissakalian, Michelson, & Dealy 1983), (Rapee 1985) (Watson, Mullett, & Pillay 1973)</p> <p>Data analysis: Effect sizes calculated pre to post-treatment and corrected for sample size.</p> <p>The included studies provide only limited application to the population targeted within the guidelines:</p> <p>Results of pre-treatment to posttreatment analysis</p> <table border="1"> <thead> <tr> <th rowspan="2">No. of Trials</th> <th colspan="3">Phobia Measures</th> <th colspan="3">Panic measures</th> <th colspan="3">Anxiety measures</th> </tr> <tr> <th>N</th> <th>Mean</th> <th>SD</th> <th>N</th> <th>Mean</th> <th>SD</th> <th>N</th> <th>Mean</th> <th>SD</th> </tr> </thead> <tbody> <tr> <td>4</td> <td>3</td> <td>.88</td> <td>(+/-) .59</td> <td>3</td> <td>1.01</td> <td>(+/-) .57</td> <td>2</td> <td>1.00</td> <td>(+/-) .30</td> </tr> </tbody> </table> <p>No pre-treatment to follow-up analysis</p> <p>Only one of these 4 studies is expanded upon in the narrative or antidepressants where it is outlined that an average of 125 mg/day in severe agoraphobic patients were assessed in a multitreatment trial. Those patients who reported spontaneous panic reported no panic attacks after 12 weeks.</p>							No. of Trials	Phobia Measures			Panic measures			Anxiety measures			N	Mean	SD	N	Mean	SD	N	Mean	SD	4	3	.88	(+/-) .59	3	1.01	(+/-) .57	2	1.00	(+/-) .30
No. of Trials	Phobia Measures			Panic measures				Anxiety measures																											
	N	Mean	SD	N	Mean	SD	N	Mean	SD																										
4	3	.88	(+/-) .59	3	1.01	(+/-) .57	2	1.00	(+/-) .30																										

Imipramine – side effects

RCT extraction table

Author (s)	Study (placebo controlled, active comparator etc.)	Type of intervention (pharmacotherapy & name of therapy) Length of study	Setting and location (primary/secondary care or other & country)	Numbers randomised Randomisation method Numbers incl in results analysis (Confirm ITT analysis or % included in results)	Inclusion criteria/ Exclusion criteria Exclusion of depression Permitted polypharmacy Washout period Substance misuse Concordance (compliance)	Mean age (years) Male/female (M/F) ratio Ethnicity	Follow-up period	Main outcome measures (extract data on primary outcome measure only and just note secondary outcome)
Mavissakalian & Perel The side effects burden of extended imipramine treatment of panic disorder <i>J Clin Psychopharmacol</i> , 2000	Placebo controlled – follow-up	Pharmacotherapy – imipramine Length of study = 24 weeks	Setting not specified in this paper. U.S. sample	110 Randomised Randomisation method not specified 100% included in analysis – ITT analysis. Where data was not present due to dropout/withdrawal, data entered as non-responder	Not elaborated here. Exclusion of depression: no concurrent or past primary major depression Permitted polypharmacy: 5 patients were receiving stable thyroid medication in euthyroid state; 17 patients started treatment while receiving benzodiazepines. Benzodiazepine recipients underwent a flexible taper at week 4, completed by week 12. 2 week placebo what out period Substance misuse not specified Concordance not specified	Mean age: 36.5 +/- 9.9 years Male/female ratio: 32%/68% (mean length of illness 9.7 +/- 2.2 years)	This 24 week study preceded a 24 week maintenance study reported in Mavissakalian & Perel 1999 <i>Arch Gen Psychiatry</i> 56: 821-7	HAM-A Physiological change (weight, pulse & blood pressure) 15 item inventory on effects of tricyclic antidepressants. For this analysis of side-effects, detail is given of: 1. sum of the side effects inventory 2. weight 3. heart rate 4. probability of endorsing four specific side effects including dry mouth, sweating drowsiness, sexual disorder 4 predictor variables 1 demographic 1 heart rate response Dose Linear quadratic change

Results: treatment, comparator data, dropouts (numbers/percentage and reasons), treatment emergent adverse events (whether spontaneous report or questioned by researcher/treating clinician), investigator's conclusions and reviewers conclusions if different from investigators

Analysis using the statistical technique of hierarchical linear modelling

	Dropouts	Before week 8	After week 8
Total	Total overall	33	18
Noncompliance		6	6
Lack of effect by week 16			9
Side Effects	30	27	3
dizziness, fatigue or sedation	9		
gastrointestinal	5		
cardiovascular	4		
Urinary retention and hesitation	2		
Sexual complaints	2		
Jerky movements	1		
Increased anxious panicky feelings	1		
Medical illness and hospitalization	1		
Flu symptoms	1		
Rash	1		
Nosebleed	1		
Increased liver enzymes	1		
Deciding to become pregnancy	1		

The side-effect sum scores (SESUM) were curvilinear, reaching a peak at week 4 (i.e. where recorded side-effects were highest) and then decreased over the subsequent 4 weeks. The change in score was statistically significant at $p < 0.01$. To illustrate, the SESUM score increase 0.42 units in week 1, 0.17 units in week 2, 0.11 units in weeks 3 and 4 and reached a peak point of 7.1 at week 4. It was then observed to decrease by 0.34 units per week for week 4 to 6 and then by 0.48 units by the following two weeks. Two other observations were made in the SESUM score, i.e. that women's scores were 1.43 units higher than men's $p < 0.05$; as the HAM-A score increased, so too did the SESUM score, by 0.34 units $p < 0.01$.

Probability of endorsing	Dry mouth	Sweating	Drowsiness	Sexual dysfunction
Demographics	Older patients more likely 1 yr inc = 5.47% OR 1.05 $p < 0.05$		Inverse relationship with age by 4.47% OR=0.95, $p < 0.01$	6.83% OR=1.06, $p < 0.01$, Females 52.5% less likely to report. OR = 0.47, $P < 0.05$
Dosage	1% (OR 1.01, $p < 0.05$)			
Heart rate response (post. Change) (one unit increase of)	11.48% (OR 1.11, $p < 0.01$)		2.96% OR = 0.97 $p < 0.05$	
Linear/quadratic change rates (as for SESUM unless stated)	$p < 0.01$	Short-term NS; long-term $p < 0.01$	$p < 0.01$	
HAM-A (one unit increase of)		7.7%, OR 1.07, $p < 0.01$	15.62% OR=1.15, $p < 0.01$	13.9% OR=1.139, $p < 0.01$

Heart rate increase from baseline was 5.59 +/- 5.77 bpm and also shows a curvilinear response as does diastolic blood pressure (not systolic blood pressure) and weight

Completers	Week 0	Week 8	Week 16	Week 24
N		77	66	59
HAM-A improvement was highly significant in the 59 completers	20.11 +/- 5.6	10.38 +/- 5.38	7.63 +/- 4.08	6.68 +/- 4.04

HAM-A improvement was highly significant in the intent to treat sample 20.25 +/- 5.75 11.68 +/- 7.84; $t[106] = 11.6$, $p < 0.0001$ (last observation carried forward)

Table of Severe Side Effects

Side effect	Baseline	Weeks 1-8	Weeks 16 and 24
Dry mouth	8.3	41.1	12.8
Sweating	6.4	23.8	13.5
Disturbed visual accommodation	0	5.6	0
Constipation	4.5	11.1	4.8
Disturbed micturation	<1	2.4	0
Tremor	6.4	8.9	<1
Ataxia	1.8	3.3	<1
Vertigo	6.4	10	<1
Nausea	9.1	6.6	0
Vomiting	1.8	1.3	0
Drowsiness	8.2	16.7	3.1
Headache	.3	7.8	3.9
Sexual disorders	5.5	5	<1
Cardiovascular symptoms	5.5	11.1	1.5
Increased energy/insomnia	15.5	7.8	3.1

Appendix 4:

Psychological interventions for panic disorder

Cognitive therapy/exposure/combined cognitive + exposure

RCT extraction table

Author (s)	Study (placebo controlled, active comparator etc.)	Type of intervention (pharmacotherapy & name of therapy) Length of study	Setting and location (primary/sec ondary care or other & country)	Numbers randomised Randomisation method Numbers incl in results analysis (Confirm ITT analysis or % included in results)	Inclusion criteria/ Exclusion criteria Exclusion of depression Permitted polypharmacy Washout period Substance misuse Concordance (compliance)	Mean age (years) Male/female (M/F) ratio Ethnicity	Follow-up period	Main outcome measures (extract data on primary outcome measure only and just note secondary outcome)
Williams & Falbo, 1996; Cognitive and performance-based treatments for panic attacks in people with varying degrees of agoraphobic disability.	3 active treatment groups and one control group	Cognitive therapy, performance-based exposure therapy, combined cognitive/performance treatment and no-treatment control group 8 weeks: 8 weekly individual 1 hour treatment sessions	Not reported, USA	Numbers randomised: 48 Randomisation method not reported All participants appear to be included in the final analysis	Included if: at least two DSM-III-R defined panic attacks/week over 2 week baseline period Exclusions not reported 25 of the 48 patients were diagnosed with major depression according to the DSM-III-R diagnostic criteria. Permitted polypharmacy: 30 subjects took prescribed medication throughout the treatment period and this was not altered. No washout period reported. No information on substance misuse reported Concordance: compliance was monitored and in the performance group 75% of subjects completed their homework assignments, in the combined group 84% completed performance assignments. Subjects in the cognitive group and in the combined group achieved equally high compliance	38 years 6/42 Ethnicity not reported	6 week follow-up (4 participants did not complete all measures) and 1-2 year follow-up (5 participants did not complete all measures)	Frequency of panic, Self-Efficacy Scales for Agoraphobia (SESA), Fear Questionnaire (FQ), anticipated panic scales, panic coping self-efficacy scale, Agoraphobic Cognitions Questionnaire (ACQ), body Sensations Questionnaire (BSQ), Beck Depression Inventory (BDI)

Funding/support: This research was supported by United States Public Health Service grant R03 MH43285.

Results: treatment, comparator data, dropouts (numbers/percentage and reasons), treatment emergent adverse events (whether spontaneous report or questioned by researcher/treating clinician), investigator's conclusions and reviewers conclusions if different from investigators

See attached pages.

Conclusions: Participants in all three active treatment groups showed significant improvement on all measures of panic, phobia and negative cognitions, post treatment. At 6 week follow-up, 69% in the cognitive group remained free of panic as did 67% in the performance group and 62% in the combined group. At long-term follow-up, 50% in the cognitive group remained free of panic, 80% in the performance group and 58% in the combined group. Those in the control group showed no improvement (control group did not complete a follow-up evaluations). Performance treatment was significantly more effective compared to cognitive therapy for FQ total phobia score, panic coping self-efficacy and ACQ. Those participants with low levels of agoraphobia showed much greater panic reduction than those with high levels of agoraphobia both at post treatment and at follow-up.

Cognitive therapy/exposure

Author (s)	Study (placebo controlled, active comparator etc.)	Type of intervention Length of study	Setting and location	Numbers randomised	Inclusion criteria/ Exclusion criteria Exclusion of depression Permitted polycharmacy	Mean age (years) Male/female (M/F) ratio Ethnicity	Follow-up period	Main outcome measures (extract data on primary outcome measure only and just note secondary outcome)
Arntz A. 2002 Cognitive therapy versus interoceptive exposure as treatment of panic disorder without agoraphobia. Behav Res Ther 2002 Mar;40(3):325-41	Cognitive Therapy compared to Interoceptive Exposure for PD without agoraphobia. A direct comparison of cognitive procedures an with exposure to feared bodily sensations. Investigates the relative efficacy of the two and the involvement of conscious considerations about the dangerousness of bodily sensations in non-cognitive treatments.	Two pre-treatment sessions followed 2 weeks later (during which patient monitored panic attacks) by 12 weekly sessions with homework. Most patients (n=54) treated individually by 15 patients were treated in groups. (Two way ANOVA showed no difference between formats and this was excluded as a variable) Cognitive Therapy (CT) based on Clark and Salkovkis approach (1986 manual) 1. cognitive model 2. hyperventilatin provocation 3. challenging dysfunctional thoughts and formulating rational thoughts 4. behavioural experiments to test catastrophic beliefs not to habituate. IE 1. Idiosyncratic functional analysis stressing role of avoidance in the maintenance of problem 2. Standard or non-standard exercises to illicit feared body sensations	Community Mental health Centre in Maastricht.	121 patients were eligible but after a 6 month wait 69 participated. N=69 4 dropouts from CT and 7 from IE before 12 th session. Randomised for condition and therapist but method not clear. Both ITT and completer analysis was carried out. ITT analysis for panic frequency was by carrying forward last observation. ITT analysis for questionnaire , no change was assumed. There was incomplete	Inclusion: <ul style="list-style-type: none"> • DSM-III-R primary diagnosis of PD with no or mild agoraphobia • PD for GE 3 months • At least one panic attack in last four weeks. • 18-69 years • No depressive disorder preceding current episode of PD or requiring acute treatment • No Behaviour therapy for PD • No organic mental disorder, mental retardation, psychotic disorders, alcohol or drug dependence, CVD, asthma, epilepsy or medical contraindications to treatment • No use of serotonergic antidepressants or benzodiazapines for at least 4 weeks OR if on agreed to stop OR if unwilling to stop keeping at constant level or stopping during the study. 8 of the CT and 11 IE group refused to stop taking medication. Medication did not influence outcome. 	Males = 42 Females = 27 Mean age = 34.8 (range 20=65) Mean duration of complaints = 5.3 years (range 5 months- 30 years)	Follow-up at 1 and 6 months post treatment	<i>Frequency of panic attacks (Definition of panic attack= sudden rise in anxiety and at least 4 sympoms)</i> Patient Assessed <ul style="list-style-type: none"> • Panic Attack Diary indicating presence/absence of DSM-III-R panic symptoms. • Patient assessed daily average level of anxiety rating (0-100) • Fear of fear questionnaire • Fear Questionnaire • STAIS • SCI-90 • Rating of 1-4 idiosyncratic assumptions formulated at first session •

Author (s)	Study (placebo controlled, active comparator etc.)	Type of intervention Length of study	Setting and location	Numbers randomised	Inclusion criteria/ Exclusion criteria Exclusion of depression Permitted polycharmacy	Mean age (years) Male/female (M/F) ratio Ethnicity	Follow-up period	Main outcome measures (extract data on primary outcome measure only and just note secondary outcome)
		3. Hierarchy of interoceptive exercises 4. Exposure exercises Therapist adherence to protocol was not formally assessed.		data on 2 completers.				
<p>Results Panic Frequency was highly skewed – logarithmic distribution is below. At 6 months, 91.7% of completers in the CT group and 80.8% of IE completers were panic free but this difference was not significant..</p> <p>Both groups improved on the measures to a similar extent with no differential efficacy as to panic frequency, daily anxiety levels and psycho-pathology complaints. There was a higher dropout rate in the IE and the therapists believed that in isolation, it was less acceptable to patients. Authors believe that as both differential effects failed to reach significance, it suggest that the two approached would be equally effective even when tested with much larger samples. Suggest combining two techniques.</p>								

RCT extraction table

Author (s)	Study (placebo controlled, active comparator etc.)	Type of intervention (pharmacotherapy & name of therapy) Length of study	Setting and location (primary/sec ondary care or other & country)	Numbers randomised Randomisation method Numbers incl in results analysis (Confirm ITT analysis or % included in results)	Inclusion criteria/ Exclusion criteria Exclusion of depression Permitted polypharmacy Washout period Substance misuse Concordance (compliance)	Mean age (years) Male/female (M/F) ratio Ethnicity	Follow-up period	Main outcome measures (extract data on primary outcome measure only and just note secondary outcome)
Hecker et al Cognitive restructuring and interoceptive exposure in the treatment of panic disorder: a crossover study In <i>Behavioural and Cognitive Psychotherapy</i> 1998, 26, 115-131	Cross-over study of two treatments	Psychological therapies: cognitive restructuring and interoceptive exposure: Length: 4 weeks in one treatment followed by 4 weeks of no contact and then 4 weeks in the other treatment= 12 weeks	Psychological Services Centre, University of Main (US)	Numbers randomised: 22 Randomisation method: not stated Numbers included in results analysis: 18 No ITT analysis. Data analysis of 18 completers (i.e. 82% of randomised patients)	Included if: met criter for panic disorder re DSM-III-R; Aged 18 yrs +; was willing to proceed after the project was explained; had a letter from their docotor indicating no medical contra-cindiations to participation. Permitted polypharmacy: anxiolytic medications but no changes allowed during study participation and stable doses had to be attained at least 3 wks prior to acceptance into study and 7 wks before treatment began Substance misuse: not stated Concordance: noted in 'dropouts' (see below)	Mean age: 42.06 years (S.D. 12.81, range 22-62) Malle/femal ratio: 17 women, 1 man Ethnicity: Caucasian	Follow-up: 1 month	Self-report: (from the Fear questionnaire) Agoraphobia avoidance (FQAG); Social phobia avoidance (FQSO); Blood injuries avoidance: (FQBI); Ratings of anxiety/depression symptoms (FQAD); global self-rating of phobic distress (FQGL). Agoraphobic Cognitions Questionnaire (ACQ). Body Sensations Questionnaire (BSQ). Trait scale of the State-Trait Anxiety Inventory. Beck Depression Inventory (BDI) Structure interview: independently & blindly assessed and 3 scores derived: panic symptoms rate (PS-Rate); Anxiety/Depression (A/D-Rate); Global Disturbance (GL-Rate) Expected Benefit: 0-8 rating scale

Results: treatment, comparator data, dropouts (numbers/percentage and reasons), treatment emergent adverse events (whether spontaneous report or questioned by researcher/treating clinician), investigator's conclusions and reviewers conclusions if different from investigators

Note: Treatment was the between-subjects factor (i.e. exposure therapy vs cognitive therapy) and trials was the within-subject factor (i.e. assessment 1,2,3). Five assessments made: 1. before treatment, 2. after first 4 treatments in block, 3. after one month of no contact, 4. after the second block of 4 sessions in the untried treatment, 5. after final one month of no contact.

There were no significant differences in the pre-treatment scores of either of the groups. Groups were assigned to either Cognitive therapy preceded exposure therapy (CT/EX) or vice versa (EX/CT)

Dropouts: Before 1st treatment: 11 or 33% of the 33 referred clients. EX/CT condition: 2 (1 completed EX x 4 sessions; 1 attended EX x 1 before dropout). CT/EX condition: 2 (1 completed CT x 4 sessions; 1 completed CT x 3)

Summary of results: Tables as presented in the paper are copied for information on baseline characteristics (table 1) and on data from measures within the first therapeutic treatment up to cross-over (table 2) and it would appear that Table 3 refers to identical data. The title of the table however indicates otherwise, where assessment #2 ought to read 4 and #3 ought to read 5. The reviewer understands table 3 therefore to refer to measures of client response before treatment, after both treatments have been administered in the cross-over design and at follow-up. Table 4 referring to the percentage of patients attaining a clinically significant outcome presents the 3 measured perspectives, i.e. 1) the independent clinician's rating of global disturbance (GD-Rate); 2) the client self-rating of global disturbance from the Fear Questionnaire (FQGL) of 2 or less and 3) a comparison with a sample of 'normal people' known as the normative sample on measures of catastrophic thinking about anxiety (ACQ) and of bodily sensations (BSQ) within 1 standard deviation of this normal sample.

Comparisons on outcome scores between the treatments were carried out using repeated measures analysis of variance. Significant trials effects were found for all the questionnaire measures except the FQSO and Trait. The former measure is mistyped in the paper as FQSQ but the reviewer understands this to be the referred to measure in the text. The most significant changes occurred between assessments 1 & 2 for all measures except the FQAG (showed continued improvement throughout) and the FQGL which showed non-significant improvement between assessments 1 & 2 and assessments 2 & 3. Structured interview data revealed significant trial effects (GL-rate: $F(1,12)=13.36, p<.005$; PS-Rate: $F(1,13)=12.23, p<.005$; A/D-Rate: $F(1, 12)=7.57, p<.05$). However, on these measures there were no significant treatment by trial interactions.

In the order of treatments comparison, repeated measures analysis of variance were again carried out for questionnaire measures. Treatment order, i.e. whether exposure therapy or whether cognitive therapy was administered first, was the between-subjects factor and, as before trials at assessment 1,4 and 5 was the within-subjects factor. Again, significant improvements were measured on all but the FQAD and Trait. There were no significant treatment by trial interaction but participants showed significant positive change between assessments 1 & 4. Nonsignificant differences were found for all questionnaire measures between assessments 4 & 5 with the exception of FQAG ($F(1,11)=6.39, p<.05$) and the FQSW ($F(1,11)=8.80, p<.05$). It was noted that the mean score at assessment 5 on the FQAG was still significantly lower than at assessment 1. However on the FQSO, the difference between participants' scores at assessments 1 and 5 was not statistically significant ($F(1,11)=0.90, p>.30$). Structured interview data analysed at assessments 1 and 5 revealed no significant treatment by trial interactions (GL-Rate: $F(1,9)=61.36, p<.001$; PS-Rate: $F(1,13)=19.89, p<.001$; A/D-Rate: $F(1,10)=5.14, p<.05$).

There were no significant differences between treatment groups on the proportion of patients to meet clinically significant improvement criteria (table 4)

Methodological limitations: Sample size very small – increased risk of type II error (i.e. of not finding a significant differences where one may indeed exist). Treatment procedures as administered in this study were very similar i.e. both treatments provided information about the disorder and models of understand the problem. The two procedures were not identical to those used in the two most well-known CBT packages for panic disorder, referred to as Barlow's Panic Control Therapy which limits the generalisability of findings. There was no direct measure of panic used in the analysis of findings despite one administered. Patients tended not to complete it if they did not have a panic attack and some only completed it if they had a panic attack. The investigators therefore abandoned it.

Conclusions: Both forms of therapy lead to improvement in measures of psychopathology associated with panic disorder. Specifically, participants showed significant improvement in catastrophic thinking (i.e. a decrease of), fear of physical sensations associated with panic, phobic avoidance and depression. Only one variable showed a difference between groups, that being participants' ratings of global disturbance within the cognitive therapy group. Findings are extremely limited due to methodological limitations.

Table 1. Client characteristics

<i>Condition</i>	<i>Sex</i>	<i>Age</i>	<i>Agoraphobia</i>	<i>Medication</i>	<i>Other Axis I</i>	<i>Month since first panic</i>
EX/CT	F	24	No	Alprazolam	-	33
EX/CT	F	58	No	Alprazolam Desipramine	MDE ¹	30
EX/CT	F	45	Mild	Alprazolam	SP ²	146
EX/CT	F	45	Mild	-	GAD ³	132
EX/CT	F	29	No	-	PTSD ⁴	1
EX/CT	F	55	No	Buspirone HCL	GAD	9
EX/CT	F	35	Mild	Alprazolam Lorazepam	-	2
EX/CT	F	41	Mild	Imipramine Alprazolam	MDE	156
EX/CT	F	39	Mod.	-	GAD	168
EX/CT		$\bar{x}=41.22$ SD=11.12				$\bar{x}=75.22$ SD=72.84
CT/EX	F	25	No	Alprazolam Lorazepam	GAD	9
CT/EX	F	32	Mild	Imipramine	MDE	24
CT/EX	F	62	Mild	Diazepam	-	8
CT/EX	F	61	No	Phenobarbital	GAD	504
CT/EX	F	46	No	Diazepam	Hypo ⁵	228
CT/EX	F	56	Mod.	Diazepam Imipramine	GAD	240
CT/EX	F	22	Mild	Alprazolam	-	9
CT/EX	M	45	Mild	Buspirone HCL	MDE	156
CT/EX	F	37	No	Imipramine Diazepam	-	12
CT/EX		$\bar{x}=42.89$ SD=14.95				$\bar{x}=132.22$ SD=170.12

Notes; ¹Major depressive episode; ²simple phobia; ³Generalised anxiety disorder; ⁴Post-traumatic stress disorder; ⁵hypochondriasis.

Table 2. Means, standard deviations, *F*-ratios and *p*-values for trials effects on questionnaire measures across assessments 1, 2 and 3

<i>Measure</i>	<i>Assessment #</i>			<i>F(df)</i>	
	<i>1</i>	<i>2</i>	<i>3</i>		
ACQ	34.67 (11.13)	30.56 (10.54)	28.61 (9.93)	6.24 (2.32)	.01
BSQ	37.11 (16.86)	30.56 (11.59)	32.50 (11.64)	3.61(2.28)	.05
FQAG	14.17 (9.09)	10.72 (9.69)	6.53 (6.56)	9.42(2.24)	.01
FQSQ	13.58 (7.90)	10.94 (6.63)	9.40 (6.08)	1.78 (2.24)	.20
FQBI	14.71 (9.09)	10.83 (8.30)	10.60 (7.63)	5.49 (2.24)	.01
FQGL	3.94 (2.21)	3.56 (1.92)	3.27 (1.87)	3.89 (2.24)	.05
FQAD	18.94 (9.96)	13.67 (7.63)	11.80 (5.80)	5.74 (2.22)	.01
AQ39	54.50 (21.08)	45.72 (16.63)	42.94 (17.00)	10.81 (2.32)	.001
BDI	14.94 (7.50)	9.44 (6.45)	11.17 (5.68)	7.68 (2.30)	.005
TRAIT	53.35	51.19	44.47	2.94 (2.24)	.10

Table 3. Means, standard deviations, *F*-ratios and *p*-values for trials effects on questionnaire measures across assessments 1, 4 and 5

<i>Measure</i>	<i>Assessment #</i>			<i>F(df)</i>	<i>P</i> <
	<i>1</i>	<i>2</i>	<i>3</i>		
ACQ	34.67 (11.13)	28.94 (11.44)	27.00 (7.64)	4.48 (2.24)	.05
BSQ	37.11 (16.86)	30.76 (12.18)	31.60 (11.62)	5.81 (2.26)	.01
FQAG	14.17 (9.09)	5.46 (6.46)	7.93 (6.68)	12.31 (2.20)	.01
FQSQ	13.58 (7.90)	6.64 (4.31)	9.27 (5.67)	3.81 (2.20)	.05
FQBI	14.71 (9.09)	8.57 (5.36)	9.87 (5.08)	3.72 (2.20)	.05
FQGL	3.94 (2.21)	2.92 (2.34)	3.38 (1.77)	4.83 (2.18)	.05
FQAD	18.94 (9.96)	13.07 (10.21)	12.85 (8.19)	2.66 (2.18)	.10
AQ39	54.50 (21.08)	41.27 (17.37)	40.13 (13.43)	11.17 (2.28)	.001
BDI	14.94 (7.50)	10.18 (6.15)	10.00 (6.40)	5.65 (2.22)	.01
TRAIT	53.35 (10.79)	47.41 (11.28)	48.40 (8.83)	2.89 (2.24)	.10

Table 4. Percentage of participants meeting criteria for clinically significant outcome from three perspectives at assessments 3 and 5

	<i>Assessment 3</i>			<i>Assessment 4</i>		
	<i>Self</i>	<i>Judge</i>	<i>Norm</i>	<i>Self</i>	<i>Judge</i>	<i>Norm</i>
EX/CT	3/9 33%	2/9 22%	4/9 44%	4/6 67%	2/8 25%	4/8 50%
CT/EX	5/8 56%	3/9 33%	4/9 44%	2/7 29%	2/6 33%	5/7 71%
All subjects	8/17 47%	5/18 28%	8/18 44%	6/13 46%	4/14 28%	9/15 60%

Cognitive therapy/exposure/relation training

RCT extraction table

Author (s)	Study (placebo controlled, active comparator etc.)	Type of intervention (pharmacotherapy & name of therapy) Length of study	Setting and location (primary/secondary care or other & country)	Numbers randomised Randomisation method Numbers incl in results analysis (Confirm ITT analysis or % included in results)	Inclusion criteria/ Exclusion criteria Exclusion of depression Permitted polypharmacy Washout period Substance misuse Concordance (compliance)	Mean age (years) Male/female (M/F) ratio Ethnicity	Follow-up period	Main outcome measures (extract data on primary outcome measure only and just note secondary outcome)
13571 Murphy et al The role of self-directed in vivo exposure in combination with cognitive therapy, relaxation training, or therapist-assisted exposure in the treatment of panic disorder with agoraphobia In <i>Journal of Anxiety Disorders</i> , Vol. 12 No. 2 pp. 117-138 1998	Active comparators	Psychological therapies: Cognitive therapy with graded exposures; Relaxation training with graded exposure or therapist assisted exposure alone Each group was also trained in self-directed exposure Length of study: 13 weeks. 2 psychological therapy sessions per week for weeks 1-3 and 1 per week for the remaining 10 weeks	Not stated in this paper – reader directed to Michelson, Marchione, Greenwals, Testa & Marchione (1996) {7561}	89 randomised Randomisation method not specified Numbers included in results = 73 No ITT analysis	Included if age of onset prior to age 40, illness of > 1 year, aged between 18 & 65 years, CGI-S score ≥ 3 (i.e. moderate to severe PDA). Excluded if current alcohol or substance abuse, organic brain syndrome, OCD or antisocial personality. Permitted polypharmacy: Non – subjects on psychoactive medication withdrawn from medication a minimum of 2 weeks prior to beginning treatment Substance misuse – stated Concordance – N/A	Mean age = 37 years Male/female ratio: 18%: 82% Ethnicity not stated	3 months	Behavioural Diary: Subjective Unit of Disturbance Scale (SUDS) (to record duration, frequency & distance travelled in ‘in vivo’ outings in phobic situations) Clinical & Self-report measures: Global Assessment of Severity scale (GAS) Standardized Behavioral Avoidance Course (5-BAC); Phobic Anxiety and Avoidance Scale; Panic attacks measured with a self-rating scale on overall severity of panic attacks; Subjective Symptom Scale (to measure agoraphobia, panic, depersonalisation and obsessions); Self-rating of Severity; Mobility Inventory; Bodily Sensations Questionnaire; Dyadic Adjustment Scale (marital satisfaction); Beck Depression Inventory
Results: treatment, comparator data, dropouts (numbers/percentage and reasons), treatment emergent adverse events (whether spontaneous report or questioned by researcher/treating clinician), investigator’s conclusions and reviewers conclusions if different from investigators								
Repeated measures ANCOVAs using pre-treatment measures as the covariate found that self-directed exposure practice decreased the number of in vivo panic attacks in all groups with slightly better results for the Cognitive Therapy group compared to the Relaxation Therapy group but this difference was not sustained at 3 month follow-up. Diary records of in vivo panic and agrophobic avoidance along with changes in outcome measures record significant decreases in panic symptoms according to DSMIII at $p < .05$ level.								

Table 1: 3 (Treatments) x 6 (Assessment Phases) Repeated Measures Analysis of Covariance (Pre-Covariate) Across Treatments and Assessment Phases

Domain	Pre-treatment		Month 1		Month 2		Month 3		Post-treatment		3-Month Follow-up		Repeated Measures <i>F</i> -Ratio	Treatment Effect <i>F</i> -Ratio	Treatment X-Repeated Measures <i>F</i> -Ratio
	M	(SD)	M	(SD)	M	(SD)	M	(SD)	M	(SD)	M	(SD)			
Assessment phase															
Weekly outings															
CT + GE	9.5	(5.7)	11.3	(4.2)	11.5	(4.2)	11.7	(4.4)	9.8	(3.3)	10.6	(4.5)			
RT + GE	9.0	(5.8)	11.4	(3.2)	11.1	(3.7)	11.0	(3.9)	11.0	(4.4)	10.1	(2.6)	8.07**	<1	5.59**
GE	8.5	(4.5)	10.9	(3.7)	11.3	(4.0)	11.1	(4.2)	9.0	(3.3)	11.1	(4.6)			
Weekly alone outings															
CT + GE	4.1	(3.7)	4.7	(2.9)	5.2	(2.9)	5.0	(3.4)	4.3	(3.6)	5.3	(3.6)			
RT + GE	3.1	(3.2)	4.7	(2.1)	4.6	(2.2)	4.5	(2.5)	4.3	(3.0)	4.9	(2.0)	9.18**	<1	<1
GE	2.9	(2.2)	4.7	(2.6)	5.0	(2.7)	5.0	(2.7)	4.4	(2.6)	6.1	(4.2)			
Practice weekly outings															
CT + GE	-	(-)	3.9	(2.6)	4.9	(3.4)	5.1	(3.7)	4.2	(3.3)	2.6	(4.4)			
RT + GE	-	(-)	3.3	(2.0)	4.7	(3.9)	4.9	(3.9)	5.5	(4.7)	1.8	(1.6)	35.43***	1.82	3.02
GE	-	(-)	5.3	(2.9)	6.1	(3.9)	6.7	(4.3)	5.6	(3.5)	2.5	(3.0)			
Weekly events															
CT + GE	20.2	(11.8)	35.4	(10.3)	35.7	(12.4)	35.4	(12.4)	33.0	(12.5)	32.0	(9.2)			
RT + GE	19.7	(17.9)	36.1	(13.7)	33.4	(10.7)	34.1	(12.3)	30.5	(9.8)	22.9	(5.2)	10.91**	<1	10.15***
GE	15.2	(11.4)	33.5	(19.5)	37.9	(20.6)	39.3	(19.0)	28.8	(13.0)	35.7	(16.0)			
Weekly alone events															
CT + GE	8.0	(7.0)	17.0	(8.4)	19.1	(9.9)	16.9	(8.4)	16.5	(11.4)	17.2	(8.1)			
RT + GE	6.4	(5.1)	17.8	(6.9)	16.9	(7.2)	17.3	(7.9)	14.7	(6.1)	13.0	(4.9)	7.21**	<1	3.08*
GE	5.8	(6.4)	16.2	(12.4)	19.0	(13.1)	20.4	(11.9)	15.6	(6.6)	20.3	(12.7)			
Practice weekly events															
CT + GE		(-)	17.5	(9.4)	20.6	(11.9)	21.4	(11.7)	19.4	(12.7)	8.9	(9.5)			
RT + GE	-	(-)	14.3	(6.5)	17.2	(7.7)	18.7	(9.6)	17.6	(9.7)	7.0	(6.2)	52.58***	3.64*	4.07*
GE		(-)	19.3	(11.4)	24.9	(15.2)	26.7	(14.9)	19.9	(9.9)	17.9	(15.2)			
In vivo anxiety															
Mean weekly SUDS															
CT + GE	2.7	(1.1)	2.5	(1.0)	2.3	(1.1)	2.1	(1.1)	1.5 ^a	(0.8)	1.0	(0.5)			
RT + GE	2.7	(1.1)	2.8	(0.7)	2.8	(0.8)	2.6	(0.8)	2.3 ^a	(0.8)	1.6	(1.0)	120.80***	3.26*	2.54
GE	3.4	(1.5)	2.8	(1.1)	2.5	(1.1)	2.4	(1.3)	1.8	(0.9)	1.5	(0.9)			
Mean weekly alone SUDS															
CT + GE	2.6	(1.4)	2.7	(1.1)	2.4	(1.2)	2.2	(1.3)	1.5 ^a	(0.9)	1.0	(0.6)			
RT + GE	2.8	(1.1)	2.9	(0.7)	2.7	(0.7)	2.5	(0.8)	2.3 ^a	(0.6)	1.6	(1.1)	99.12***	2.08	1.92
GE	3.1	(1.7)	2.8	(1.1)	2.6	(1.2)	2.4	(1.3)	1.9	(1.1)	1.7	(0.8)			

Domain	Pre-treatment		Month 1		Month 2		Month 3		Post-treatment		3-Month Follow-up		Repeated Measures <i>F</i> -Ratio	Treatment Effect <i>F</i> -Ratio	Treatment X-Repeated Measures <i>F</i> -Ratio
	M	(SD)	M	(SD)	M	(SD)	M	(SD)	M	(SD)	M	(SD)			
Diary Measure															
Mean weekly accompanied SUDS															
CT + GE	2.8	(1.1)	2.3	(1.1)	2.2	(1.1)	1.9	(1.1)	1.5	(0.9)	0.9	(0.4)			
RT + GE	2.7	(1.2)	2.8	(0.9)	2.9	(0.8)	2.6	(0.9)	2.3	(0.8)	1.8	(1.0)	103.97***	5.46**	1.50
GE	3.7	(1.6)	2.7	(1.1)	2.4	(1.1)	2.4	(1.2)	1.9	(0.9)	1.5	(0.9)			
Peak weekly SUDS															
CT + GE	5.7	(1.4)	5.5	(1.0)	5.3	(0.8)	4.8	(1.4)	3.8	(1.5)	3.6	(1.3)			
RT + GE	5.6	(1.3)	5.7	(0.8)	5.5	(1.0)	5.1	(0.8)	4.2	(0.9)	3.0	(1.6)	199.41***	<1	2.83
GE	6.1	(1.2)	5.8	(1.1)	5.2	(1.3)	4.9	(1.5)	4.6	(1.6)	3.7	(1.2)			
Peak weekly alone SUDS															
CT + GE	4.1	(1.9)	5.0	(1.1)	4.7	(0.9)	4.2	(1.5)	3.1	(1.4)	2.8	(1.6)			
RT + GE	4.4	(1.7)	4.9	(0.7)	4.7	(0.8)	4.5	(0.8)	4.1	(1.1)	2.4	(1.5)	173.26***	<1	3.71*
GE	4.6	(1.8)	5.1	(1.1)	4.8	(1.5)	4.3	(1.7)	3.5	(1.5)	3.4	(1.2)			
Peak weekly accompanied SUDS															
CT + GE	5.1	(1.7)	4.7	(1.3)	4.3	(1.1)	3.9	(1.4)	3.3	(1.6)	2.6	(1.0)			
RT + GE	4.8	(1.7)	5.0	(1.1)	5.0	(1.1)	4.4	(1.1)	3.9	(0.9)	3.2	(1.5)	134.57***	2.63	1.21
GE	5.0	(1.6)	5.2	(1.3)	4.6	(1.4)	4.4	(1.5)	4.1	(1.8)	3.2	(1.4)			
Practice mean weekly alone SUDS															
CT + GE	-	(-)	3.1	(0.9)	2.6	(1.1)	2.4	(1.3)	1.6 ^a	(0.7)	1.0	(0.3)			
RT + GE	-	(-)	2.9	(0.8)	2.9	(0.8)	2.8	(0.8)	2.8 ^a	(1.8)	1.3	(0.3)	130.36***	3.73*	4.06*
GE	-	(-)	2.9	(1.1)	2.8	(1.2)	2.6	(1.2)	2.2	(1.0)	2.0	(0.7)			
Practice mean weekly accompanied SUDS															
CT + GE	-	(-)	2.8	(1.1)	2.5	(1.1)	2.2	(1.2)	1.8	(1.0)	1.4	(0.6)			
RT + GE	-	(-)	3.3	(1.0)	3.2	(0.9)	2.9	(0.9)	2.5	(0.8)	1.8	(1.0)	67.72***	3.75*	1.18
GE	-	(-)	2.9	(1.3)	2.1	(1.2)	2.6	(1.3)	2.3	(1.0)	1.9	(0.9)			
Time out															
Total weekly time out															
CT + GE	2.86	(.31)	3.01	(.18)	3.02	(.21)	3.06	(.17)	3.07	(.14)	3.06	(.15)			
RT + GE	2.66	(.89)	3.05	(.19)	3.11	(.19)	3.09	(.20)	3.04	(.22)	3.00	(.24)	5.70*	<1	3.56*
GE	2.87	(.29)	2.96	(.24)	3.01	(.24)	3.09	(.19)	3.02	(.21)	3.08	(.18)			
Mean weekly time out per event															
CT + GE	1.70	(.32)	1.51	(.15)	1.51	(.10)	1.55	(.14)	1.60	(.16)	1.59	(.14)			
RT + GE	1.59	(.57)	1.54	(.15)	1.61	(.15)	1.59	(.15)	1.59	(.19)	1.64	(.16)	21.08***	<1	4.96**
GE	1.85	(.31)	1.55	(.19)	1.54	(.16)	1.57	(.12)	1.64	(.18)	1.60	(.15)			

Domain	Pre-treatment		Month 1		Month 2		Month 3		Post-treatment		3-Month Follow-up		Repeated Measures <i>F</i> -Ratio	Treatment Effect <i>F</i> -Ratio	Treatment X-Repeated Measures <i>F</i> -Ratio
	M	(SD)	M	(SD)	M	(SD)	M	(SD)	M	(SD)	M	(SD)			
Mean weekly alone time out															
CT + GE	2.11	(.64)	2.49	(.28)	2.57	(.28)	2.60	(.22)	2.55	(.43)	2.58	(.33)			
RT + GE	1.95	(.97)	2.58	(.22)	2.64	(.21)	2.62	(.23)	2.48	(.57)	2.55	(.38)	5.65*	<1	1.19
GE	1.91	(.73)	2.43	(.30)	2.57	(.30)	2.66	(.28)	2.58	(.36)	2.50	(.61)			
Mean weekly alone time out per event															
CT + GE	1.41	(.47)	1.33	(.17)	1.37	(.16)	1.42	(.18)	1.44	(.20)	1.44	(.19)			
RT + GE	1.31	(.66)	1.38	(.15)	1.46	(.19)	1.46	(.18)	1.38	(.35)	1.49	(.23)	6.40**	<1	3.07*
GE	1.36	(.52)	1.36	(.19)	1.42	(.18)	1.46	(.16)	1.47	(.21)	1.30	(.33)			
Mean weekly accompanied time out															
CT + GE	2.44	(.97)	2.82	(.20)	2.80	(.22)	2.85	(.20)	2.84	(.19)	2.81	(.20)			
RT + GE	2.47	(.90)	2.81	(.29)	2.90	(.27)	2.87	(.25)	2.74	(.62)	2.69	(.60)	4.21*	<1	1.50
GE	2.74	(.35)	2.78	(.28)	2.79	(.25)	2.85	(.21)	2.64	(.65)	2.84	(.29)			
Mean weekly accompanied time out per event															
CT + GE	1.60	(.56)	1.61	(.18)	1.65	(.18)	1.65	(.19)	1.72	(.18)	1.68	(.12)			
RT + GE	1.64	(.61)	1.64	(.20)	1.73	(.18)	1.69	(.16)	1.60	(.40)	1.63	(.43)	1.41	<1	1.55
GE	1.92	(.31)	1.68	(.19)	1.64	(.19)	1.68	(.13)	1.71	(.44)	1.77	(.15)			
Practice mean weekly alone time out															
CT + GE	-	(-)	2.18	(.53)	2.36	(.32)	2.39	(.30)	2.01	(1.0)	1.47	(1.0)			
RT + GE	-	(-)	2.32	(.25)	2.43	(.28)	2.42	(.31)	2.21	(0.7)	1.53	(1.0)	33.21**	2.59	3.04*
GE	-	(-)	2.24	(.38)	2.45	(.36)	2.49	(.40)	2.40	(0.7)	2.01	(0.9)			
Practice mean weekly accompanied time out															
CT + GE	-	(-)	2.21	(.55)	2.41	(.30)	2.58	(.24)	2.14	(1.0)	1.70	(1.1)			
RT + GE	-	(-)	2.18	(.42)	2.48	(.39)	2.52	(.36)	2.37	(0.9)	1.90	(1.0)	28.38**	2.02	1.06
GE	-	(-)	2.45	(.45)	2.54	(.42)	2.68	(.31)	2.38	(0.8)	2.20	(1.0)			
Distance travelled															
Mean weekly distance															
CT + GE	1.61	(.57)	2.05	(.29)	2.03	(.36)	2.13	(.37)	2.07	(.32)	2.18	(.27)			
RT + GE	2.06	(.47)	2.00	(.31)	2.11	(.35)	2.10	(.29)	2.12	(.36)	2.12	(.38)	7.40**	<1	1.61
GE	1.60	(.47)	1.93	(.36)	2.03	(.33)	2.07	(.28)	1.99	(.34)	2.08	(.31)			
Mean weekly distance per event															
CT + GE	0.58	(.21)	0.66	(.23)	0.64	(.19)	0.72	(.28)	0.71	(.23)	0.78	(.17)			
RT + GE	0.40	(.38)	0.63	(.20)	0.72	(.28)	0.71	(.23)	0.78	(.31)	0.88	(.30)	21.58***	1.76	2.42
GE	0.70	(.38)	0.63	(.19)	0.64	(.24)	0.64	(.16)	0.69	(.20)	0.69	(.21)			
Mean weekly alone distance															
CT + GE	1.12	(.67)	1.47	(.49)	1.53	(.53)	1.64	(.54)	1.71	(.49)	1.71	(.23)			
RT + GE	1.51	(.56)	1.56	(.48)	1.60	(.47)	1.63	(.40)	1.59	(.51)	1.71	(.45)	15.96***	<1	1.87
GE	1.06	(.55)	1.38	(.47)	1.59	(.39)	1.68	(.36)	1.65	(.31)	1.67	(.30)			

Domain	Pre-treatment		Month 1		Month 2		Month 3		Post-treatment		3-Month Follow-up		Repeated Measures <i>F</i> -Ratio	Treatment Effect <i>F</i> -Ratio	Treatment X-Repeated Measures <i>F</i> -Ratio
	M	(SD)	M	(SD)	M	(SD)	M	(SD)	M	(SD)	M	(SD)			
Mean weekly alone distance per event															
CT + GE	0.45	(.28)	0.50	(.22)	0.53	(.25)	0.63	(.34)	0.70	(.26)	0.72	(.20)			
RT + GE	0.75	(.33)	0.50	(.29)	0.55	(.31)	0.56	(.29)	0.58	(.31)	0.75	(.32)	41.17***	<1	4.40*
GE	0.49	(.25)	0.48	(.19)	0.58	(.28)	0.60	(.20)	0.66	(.23)	0.55	(.15)			
Mean weekly accompanied distance															
CT + GE	1.47	(.57)	1.83	(.28)	1.79	(.34)	1.87	(.31)	1.61	(.45)	1.93	(.40)			
RT + GE	1.73	(.57)	1.69	(.43)	1.85	(.53)	1.89	(.35)	1.96	(.39)	1.94	(.43)	5.06*	<1	3.60*
GE	1.53	(.50)	1.71	(.41)	1.76	(.38)	1.77	(.32)	1.65	(.57)	1.89	(.34)			
Mean weekly accompanied distance per event															
CT + GE	0.58	(.23)	0.74	(.27)	0.70	(.19)	0.75	(.25)	0.64	(.23)	0.86	(.25)			
RT + GE	0.85	(.47)	0.62	(.24)	0.73	(.31)	0.80	(.27)	0.85	(.31)	0.98	(.34)	23.05***	2.04	6.19**
GE	0.76	(.42)	0.69	(.23)	0.67	(.25)	0.67	(.17)	0.73	(.32)	0.77	(.21)			
Practice mean weekly alone distance per event															
CT + GE	-	(-)	0.41	(.31)	0.43	(.25)	0.53	(.24)	0.56	(.15)	0.64	(.27)			
RT + GE	-	(-)	0.51	(.25)	0.51	(.27)	0.58	(.26)	0.54	(.27)	0.62	(.20)	16.63***	<1	8.83***
GE	-	(-)	0.40	(.21)	0.55	(.28)	0.56	(.22)	0.65	(.25)	0.45	(.15)			
Practice mean weekly accompanied distance per event															
CT + GE	-	(-)	0.63	(.43)	0.56	(.29)	0.62	(.29)	0.52	(.27)	0.69	(.29)			
RT + GE	-	(-)	0.52	(.37)	0.63	(.34)	0.81	(.40)	0.91	(.42)	0.52	(.24)	8.00*	1.07	9.33***
GE	-	(-)	0.58	(.28)	0.63	(.24)	0.67	(.20)	0.82	(.44)	0.61	(.24)			

Note. M = mean; SD = standard deviation; CT = cognitive therapy; GE = therapist-directed graduated exposure; RT= relaxation therapy; SUDS = Subjective Unit of Distress Scale (-) = No data for that assessment phase.

*Significantly different ($p < .05$).

* $p < .05$. ** $p < .01$. *** $p < .001$.

Interoceptive exposure/breathing retraining

RCT extraction table

Author (s)	Study (placebo controlled, active comparator etc.)	Type of intervention (pharmacotherapy & name of therapy) Length of study	Setting and location (primary/secondary care or other & country)	Numbers randomised Randomisation method Numbers incl in results analysis (Confirm ITT analysis or % included in results)	Inclusion criteria/ Exclusion criteria Exclusion of depression Permitted polypharmacy Washout period Substance misuse Concordance (compliance)	Mean age (years) Male/female (M/F) ratio Ethnicity	Follow-up period	Main outcome measures (extract data on primary outcome measure only and just note secondary outcome)
Craske et al 1997 Interoceptive exposure versus breathing retraining within cognitive-behavioural therapy for panic disorder with agoraphobia In <i>British Journal of Clinical Psychology</i> 1997, 36, 85-99	Active comparator	Psychological therapy: Cognitive restructuring, interoceptive exposure and in vivo exposure to agoraphobic situations (CIE) vs cognitive restructuring, breathing retraining and in vivo exposure to agoraphobic situations (CBE) Length of study: 12 weeks	Self-referred or referred by mental health professionals to the UCLA Anxiety Disorders Behavioral Program	Numbers randomised= 50 Randomisation method not specified Numbers included in results: 38 No ITT analysis: 76% included in the analysis	Included if: principal diagnosis of PDA, rated as ≥ 4 on distress/impairment scale, absence of suicidality psychosis, organic brain damage or current (last 6 months) substance abuse. 55% were stabilized on medications: 29% on anxiolytics, 5% on antidepressants, 21% on combination of anxiolytic, antidepressants and beta-blockers (and were instructed to remain on medications throughout).	Mean age=33.8 years (10.7; range 22-48) Male/female ratio: 47% /53% Caucasians: 84%	Follow-up: 6 months	Clinician ratings: ADIS-R Self-report questionnaire: Anxiety sensitivity index (ASI) Mobility Inventory (MI) Situational Fear Questionnaire (SFQ); SCL-90; Subjective Symptoms Scale (SSL); Fear & Avoidance Hierarchies (10 items rated 0-8) Self-monitoring: Panic attack records (expected vs. unexpected rated 0-8) of intensity, symptoms. Behavioural measures: Situational behavioural approach tests (BAT)

Results: treatment, comparator data, dropouts (numbers/percentage and reasons), treatment emergent adverse events (whether spontaneous report or questioned by researcher/treating clinician), investigator's conclusions and reviewers conclusions if different from investigators

Dropouts: 9 in total, 6 did not give a reason and 3 for financial/time commitments, 3 due to worsening depression. 7 from CIE. 4 dropped out and 1 patient was removed from CBE.

CIE patients fared better on panic frequency ($F(1,29)=6.8, p<.02$) fewer unexpected panics ($F(1,29)=7.6, p<.01$) and fewer panics over the last month ($F(1,35)=5.5, p=.025$) than did CBT patients. ANCOVAs yielded group differences at post-treatment on each measure.

There were no significant differences in panic apprehension at post treatment

There was significant decrease in all measure from pre to post treatment on panic fear and avoidance for the CIE but not the CBE group (ts 3.0 to 4.8, ps .001 to .012). ANOVAs did not yield group differences at post-treatment. On agoraphobic fear and avoidance, ANCOVAs did not yield group differences at post-treatment. Within both CIE and CBE treatments, all measures decreased significantly from pre- to post-treatment apart from Mobility Inventory in the CIE group and agoraphobia and social phobia SFQ subscales in the CBE group.

Measurement of General Distress with the HAS recorded significant differences from pre- to post-treatment and the SCL-90-R subscale in both the CIE and CBE groups but the CBE recorded significant differences in the Hamilton Depression scale as well. CIE and CBE respectively were: CIE ts 3.2 to 8.1, ps .000 to .009; CBE ts 3.2 to 5.4, ps .000 to .007.

On measures of overall severity and impairment data reported appear contradictory. A record of the investigators narrative is given verbatim to avoid confusion: 'ANCOVAs yielded significantly less severity ($F(1,37)=14.7, p<.01$) and less SSS ($F(1,27)=6.6, p<.02$) for CIE versus CBE at post-treatment. Within CIE, both measures decreased significantly from pre- to post-treatment (ts 4.3 and 16.5, ps .000 and .001). the same occurred within CBE (ts = 2.6 and 7.5, ps .000 and .02)'

Clinically significant change

More of the CIE group attained panic free status ($z=2.62, p<.05$) and were assigned a diagnostic severity rating of 2 or less ($z=3.26, p<.01$). Overall, 'composite recovery' rates did not differ significantly between groups.

Follow-up

It is stated that no funds were available for follow-up participation and hence only 75% of CIE and 72% of CBE participants had recorded follow-up data

Panic frequency: Fewer panics reported on each measure in CIE group (ts 2.6 to 4.7, ps .001 to .04). the CBE participants reported fewer panics in the last month only (but it is not stated whether this is the last month of therapy or the last month of study participation) ($t(13)=2.4, p<.04$).

Panic apprehension: Only ASI decreased from pre-treatment to follow-up in the CBE group ($t(9)=3.4, p<.02$) whereas within the CIE group, all measures recorded a decrease in panic apprehension (ts 4.2 to 5.2, ps .003 to .004).

Panic fear and avoidance: Both groups recorded significant decreases from pre-treatment to follow-up on this measure (ts 3.0 and 3.2, ps .01 and .02)

Agoraphobic fear and avoidance: Both groups recorded significant decreases from pre-treatment to follow-up on all measures. CIE and CBE respectively: ts 2.4 to 8.0, ps .000 to .05; CBE ts 2.6 to 7.4, ps .000 to .03 but CIE participants reported less fear of agoraphobic situations than did CBE participants.

General distress: CIE participants rated less anxiety than CBE patients at follow-up ($F(1,15)=9.6, p<.01$). Significant decreases were recorded on all measures for both groups respectively as follows: CIE ts 2.5 to 6.6, ps .000 to .05; CBE ts 3.4 to 5.5, ps .000 to .02 apart from depression for both groups and SCL-90-R anxiety for the CBE group.

Overall severity and impairment: although both groups decreased significantly from pre-treatment to follow-up: CIE ts 3.3 and 8.5, ps .000 and .01; CBE ts 2.7 and 4.4, ps .001 and .03. However, CIE participants rated less SSS than CBE participants at follow-up ($F(1,19)=7.8, p<.02$)

Conclusion: Interoceptive exposure was more efficacious than breathing retraining, on certain measures, when each was combined with cognitive restructuring and in vivo exposure. These effects were manifested in decrease in panic frequency, overall severity and functioning at post-treatment and follow-up. The follow-up data is limited due to rates of attrition.

EMDR/EFER

RCT extraction table

Author (s)	Study (placebo controlled, active comparator etc.)	Type of intervention (pharmacotherapy & name of therapy) Length of study	Setting and location (primary/sec ondary care or other & country)	Numbers randomised Randomisation method Numbers incl in results analysis (Confirm ITT analysis or % included in results)	Inclusion criteria/ Exclusion criteria Exclusion of depression Permitted polypharmacy Washout period Substance misuse Concordance (compliance)	Mean age (years) Male/female (M/F) ratio Ethnicity	Follow-up period	Main outcome measures (extract data on primary outcome measure only and just note secondary outcome)
Feske & Goldstein, 1997; Eye movement desensitisation and reprocessing treatment for panic disorder: a controlled outcome and partial dismantling study.	3 arms including waiting list control	Eye movement desensitisation and reprocessing (EMDR), eye fixation exposure and reprocessing (EFER) and waiting list control 3 week treatment period average	Outpatients, USA	43 initially selected, 3 dropped out so 40 were randomised to treatment groups Randomisation method not reported 36 of 40 provided post treatment data and 28 were included in the follow-up sample	Included if: at least one panic attack recorded during 2 week pre-test monitoring period and panic disorder for at least 1 year; concurrent psychotherapy suspended for duration of the study, those in follow-up assessment were included only if they did not receive additional psychological or pharmacological treatment during follow-up period; psychotropic medication was on a stable dosage. Excluded if: SCID-I diagnosis of current or past psychosis, organic mental disorder, current alcohol or substance dependence, obsessive-compulsive disorder, SCID-II diagnosis of paranoid, schizoid, schizotypal, borderline, or antisocial personality disorder, major depression if of greater severity than panic disorder or accompanied by suicidal ideation/ daily dose of ≥ 1.5 mg alprazolam or equivalent No washout period reported 43 participants entered the study, 5 (11.6%) dropped out (1 from each treatment group and 3 prior to randomisation)	35.2 years 9/31 Caucasian 34 African American 6	3 months	Agoraphobic Cognitions Questionnaire (ACQ), Body Sensations Questionnaire (BSQ), Mobility Inventory for Agoraphobia (MI), Beck Anxiety Inventory (BAI), Panic Appraisal Inventory (PAI) Secondary outcome measures included Beck Depression Inventory, Brief Symptom Inventory and Social Adjustment Scale
Funding/Support: This research was supported in part by a National Institute of Mental Health Grant (R21-MH49851)								
Results: treatment, comparator data, dropouts (numbers/percentage and reasons), treatment emergent adverse events (whether spontaneous report or questioned by researcher/treating clinician), investigator's conclusions and reviewers conclusions if different from investigators								
See attached pages								
Conclusions: EMDR was more effective than waiting list control post test but EMDR significantly more effective than EFER for only two of the four composite measures. At three month follow-up, there were no significant differences between the EMDR and the EFER groups.								

Psychological interventions

Cognitive therapies

Meta analysis/systematic review extraction table

Author (s)	Research question	Review type Databases used Time period covered Data analysis	Study design Interventions Follow-up period	Numbers randomised Randomisation method Numbers incl in results analysis (Confirm ITT analysis or % included in results)	Total sample number Age (mean/SD/range) Male/female Ethnicity	Outcomes
<p>Oei, Llamas & Devilly 1999</p> <p>The efficacy and cognitive processes of cognitive behaviour therapy in the treatment of panic disorder with agoraphobia</p>	<p>Evaluation of the effectiveness of CBT for GAD and to evaluate whether the efficacy of CBT treatments is related to the change to cognitive processes that are postulated to be important in the cognitive models of PDA.</p>	<p>Systematic review with some meta-analysis</p> <p>Time period: 1969-1996 divided between two searches: 1969-1989 and 1990 to 1996</p> <p>Only 1 included study pre-dates DSM-III (Emmelkamp et al 1978)</p> <p>Data analysis – qualitative review and meta-analysis</p> <p>Databases searched: PsycLit CD, Carl online</p>	<p>Study designs included 17 RCTs and the rest were group comparison, single case-study, multiple baseline across subjects, post hoc design, cross-over, sequential staggering of treatment conditions, time series and repeated measures</p> <p>Interventions:</p> <p>CBT approaches: cognitive restructuring and training, self-statement training, paradoxical intervention, covert rehearsal of coping with anxiety, reattribution of somatic symptoms, coping thoughts training, thought stopping, breathing and relaxation training and variations of prolonged exposure</p> <p>26 of 35 studies included follow-up from 1 to 16 months after termination of treatment</p>	<p>No total of numbers randomised 908 (from 17 studies employing randomisation.</p>	<p>Total sample number: 1317</p> <p>Male/Female: 19.73%/80.27%</p>	<p>A variety of unspecified outcome measures assessed changes in:</p> <p>Panic</p> <p>Fear and avoidance</p> <p>Severity/intensity: SUD scales and global assessment of severity scale</p> <p>General anxiety:</p> <p>Social anxiety</p> <p>General symptomatology</p> <p>Behavioural</p> <p>Cognitive</p> <p>Physiological</p> <p>Locus of control</p> <p>Depression</p> <p>Marital state</p> <p>Assertiveness</p> <p>Endstate functioning</p>

Author (s)	Research question	Review type Databases used Time period covered Data analysis	Study design Interventions Follow-up period	Numbers randomised Randomisation method Numbers incl in results analysis (Confirm ITT analysis or % included in results)	Total sample number Age (mean/SD/range) Male/female Ethnicity	Outcomes
Results: treatment, comparator data, dropouts (numbers/percentage and reasons), treatment emergent adverse events (whether spontaneous report or questioned by researcher/treating clinician), investigator's conclusions and reviewers conclusions if different from investigators						
Outcome measure		% of studies employing that measure	% of studies sig. Improvement by post-treatment and/or follow-up			
Panic		60	100			
Fear and avoidance		77	100			
Severity/intensity		46	100			
General anxiety		44	90			
Social anxiety		14	28.6			
General symptomatology		26	100			
Behavioural		46	96			
Cognitive		46	98			
Physiological		14	4 recorded heart rate and 1, skin conductance. Sign improvement in heart rate. 2 studies reported significant improvement, 1 reported disimprovement, 1 inconsistent results and 1 improvement only after 3 months follow-up			
Locus of control		20	100			
Depression		66	100			
Marital state		4 studies	One study showed improvement, one disimprovement, one mixed and one no difference			
Assertiveness		14	100			
Endstate functioning		28.5	100			
Meta-analysis of studies employing the Fear Questionnaire – Agoraphobia subscale (11 studies)						
Author's conclusions: The results show that CBT is an effective treatment for PDA.						

Table 3 Pre, post and follow-up means and effect size scores for the FQ agoraphobia subscale scores for studies in the meta-analysis

Study	Pre-test mean	Effect size 1	Effect size 2	Post-test mean	Effect size 1	Effect size 2	F/up mean	Effect size 1	Effect size 2
Barlow et al (1984)	27.00	4.60	1.76	17.90	2.67	0.70			
Beck et al (1994)	(1) 13.07	1.65	0.15	5.73	0.09	-0.71			
	(2) 11.50	1.32	-0.03	10.06	1.01	-0.21			
	(3) 9.77	0.95	-0.24	9.62	0.92	-0.26			
Chambless et al (1986)	26.39	4.47	1.69	12.09	1.44	0.03	10.09	1.01	0.56
de Beurs et al (1995)	32.90	5.87	2.45	22.20	3.74	1.29			0.05
Marchione et al (1987)	29.80	5.19	2.09	10.6	1.12	-0.14			0.14
Mavissakalian et al (1983)	(1) 22.0	3.55	1.18	17.7	2.64	0.68	12.30	1.49	-*0.11
	(2) 23.0	3.77	1.30	13.6	1.77	0.21	13.00	1.64	
Michelson et al (1988)	28.0	4.83	1.88	8.60	0.70	-0.38	10.90	1.19	
Michelson et al (1990)	12.11	1.43	0.03	3.56	-0.38	-0.96			
Ost et al (1993)	(1) 25.20	4.23	1.56	12.60	1.55	0.09	11.80	1.38	0.00
	(2) 27.27	4.67	1.80	11.53	1.33	-0.03	12.40	1.78	0.07
	(3) 26.80	4.57	1.74	15.80	2.23	0.47	14.60	1.98	0.33
Swinson et al (1995)	(1) 25.50	4.30	1.59	17.30	2.55	0.64	}15.69	2.19	0.45
	(2) 27.65	4.76	1.84	27.18	4.66	1.79			
Williams & Rappoport (1983)	(1) 22.60	3.68	1.25	16.80	2.45	0.58	15.80	2.23	0.46
	(2) 24.10	3.97	1.43	16.00	2.25	0.48	15.40	2.13	0.42

Note: Effect size 1 is the means of the studies compared with Trull and colleagues (1988) college norms for the FQ agoraphobia subscale, and effect size 2 is the means of the studies compared to the general (community) population norms for the FQ agoraphobia subscale.

Meta-analysis of studies employing the Fear Questionnaire – Total (7 studies)

Table 4 Pre, post and follow-up means and effect size scores for the FQ total scale scores for studies in the meta-analysis

Study	Pre-test mean	Effect size 1	Effect size 2	Post-test mean	Effect size 1	Effect size 2	F/up	Effect size 1	Effect size 2
Marchione et al. (1987)	67.60	3.01	1.67	22.20	-0.42	-1.12	-	-	-
Mavissakalian et al. (1983)	(1) 51.9 (2) 47.4	1.83 1.49	0.71 0.43	45.1 29.1	1.31 0.10	0.29 -0.70	36.9 27.9	0.69 0.01	-0.22 -0.77
Michelson et al (1988)	59.50	2.40	1.17	26.10	-0.12	-0.88	29.30	0.12	-0.69
Michelson et al (1990)	63.00	2.66	1.39	32.78	0.38	-0.47	-	-	-
Ost et al (1993)	(1) 52.27 (2) 52.07 (3) 51.47	1.85 1.84 1.79	0.73 0.72 0.68	32.87 28.40 32.33	0.39 0.05 0.35	-0.47 -0.74 -0.50	30.00 27.80 28.47	0.22 0.01 0.06	-0.64 -0.78 -0.74
Salkovskis et al. (1986)	53.20	1.92	1.17	28.44	0.06	-0.74	25.11	-0.20	-0.16
Williams & Rappoport (1983)	(1) 56.10 (2) 57.80	2.14 2.27	0.96 1.07	41.00 41.40	1.00 1.03	0.03 0.06	41.01 36.60	1.01 0.67	0.04 -0.24

Note: Effect size 1 is the means of the studies compared with Trull and colleagues (1988) college norms for the FQ total scale, and effect size 2 is the means of the studies compared to the general (community) population norms for the FQ total scale.

Table of included studies. NOTE: studies numbered 2, 4, 5, 6, 10, 13, 16, 20-25, 29, 32, 33 35 were RCTs

RCT extraction table

Author (s)	Study (placebo controlled, active comparator etc.)	Type of intervention (pharmacotherapy & name of therapy) Length of study	Setting and location (primary/secondary care or other & country)	Numbers randomised Randomisation method Numbers incl in results analysis (Confirm ITT analysis or % included in results)	Inclusion criteria/ Exclusion criteria Exclusion of depression Permitted polypharmacy Washout period Substance misuse Concordance (compliance)	Mean age (years) Male/female (M/F) ratio Ethnicity	Follow-up period	Main outcome measures (extract data on primary outcome measure only and just note secondary outcome)
Petterson & Cesare, 1996	CBT vs. control	Cognitive behaviour therapy (six weekly sessions) Study length 6 weeks	Not reported, USA	Total randomised = 27 Randomisation method= not reported Not clear how many patients were initially randomised and how many included in final results	Included if: subjects met the criteria for panic disorder according to the Anxiety Disorder Interview Schedule-revised No other inclusion/exclusion criteria stated No polypharmacy, washout period, substance misuse or concordance information reported	Mean age; male/female ratio Treatment group: 40.21 (SD not reported); 6/8 Control group: 35.54 (SD not reported); 4/9 Ethnicity not reported:	No follow-up period after 6 week study period reported	Anxiety Sensitivity Index (ASI), State trait Anxiety Inventory (STAI), Panic Attack Record Also reported as secondary outcomes were physiological arousal in terms of blood pressure, pulse rate and finger temperature.
<p>Results: treatment, comparator data, dropouts (numbers/percentage and reasons), treatment emergent adverse events (whether spontaneous report or questioned by researcher/treating clinician), investigator's conclusions and reviewers conclusions if different from investigators</p> <p>ASI: Time main effect (F (1,25)= 13.08, p<0.001) post-test mean=29.05 significantly different from pre-test mean (mean=36.15). Treatment by Time interaction was significant (F (1,25)= 15.15, p<0.001)</p> <p>STAI: Treatment by Time interaction (F (1,25)=6.81, p<0.05), mean not reported</p> <p>Panic Attack Record: Time main effect (F (1,25)= 8.03, p<0.01), mean post-test was 1.62 and significantly less than pre-test mean=2.55. Treatment by Time interaction was significant (F (1,25)=21.93, p<0.001)</p> <p>Also reported were physiological measures. There were no statistical differences between the pre-test and post test for the physiological indices (blood pressure, pulse and finger temperature)</p> <p>Conclusion: CBT appeared to be effective in decreasing panic disorder for all three measures, ASI, STAI and number of panic attacks compared to the control group.</p>								

Predicting patients who drop out

Author (s)	Study Design	Comparisons	Setting and location	Numbers of participants	Inclusion criteria/ Exclusion criteria	Characteristics of participants	Follow-up period	Main outcome measures Analysis
Keijsers et al Prediction of drop out in CBT for PD Behaviour Therapy 2001	Observational study to prospectively identify which of four possible groups of patients are more likely to drop out of treatment	The four groups proposed are: Lower level of education Treatment motivation Personality psychopathology Initial treatment severity	Dutch psychology OPD	161 patients started treatment 32 (19.9%) dropped out.	<u>Inclusion criteria</u> DSM IV 18 -65 Agreement to be assessed for research <u>Exclusion criteria</u> Schizophrenia, organic brain disorder, mental retardation, alcohol/psychoactive drug misuse, current treatment by other therapists Patients on anti-depressants were stopped and washed out for 2 weeks	Not described	n/a	Drop out rate – defined as not completing the 15 50 minute sessions planned by the therapists.

Results

What the patients said:

7 drop outs failed to provide an explanation for dropping out
 7 considered themselves sufficiently improved
 6 stopped for personal/scheduling reasons
 4 stopped because the therapist changed
 17 stopped because of lack of motivation, dissatisfaction with CBT, dissatisfaction with gain up to that point.
 Several gave more than one reason for stopping.

What the authors said:

There was no statistical difference between the groups identified (education, treatment motivation, personality psychopathology, and initial symptom severity, to explain why patients dropped out. They did identify that level of education and motivation were significant to predict drop out but the effect size was low

The message:

There is no evidence that the therapists were blinded to the possible groups prior to treatment – so that they may have influenced the outcome
 The lack of finding a predicting variable to explain dropout is a negative result – of variable importance
 The drop out rate is lower than with general psychological treatments in “ordinary” OPDs 20% vs. 30% – 60%
 I am not sure how helpful this study is.

Different levels of contact time

Author (s)	Study Design	Comparisons	Setting and location	Numbers of participants	Inclusion criteria/ Exclusion criteria	Characteristics of participants	Follow-up period	Main outcome measures Analysis
Sharp et al Reduced therapist contact in CBT for PD and agoraphobia in primary care; global measures of outcome in a randomised controlled trial BJGP 2000 50 963-968	Randomised trial between standard therapist contact, minimum therapist contact, and bibliotherapy. One therapist provided intervention – another (blinded) therapist provided assessment.	All patients received the same CBT, and same treatment instructions, and same manual Generally used Barlow type treatment objectives/methodology 3 levels of therapist contact: 1. Standard: 8 sessions of 45 mins, over 12 weeks – total 6 hours 2. Minimum: 6 sessions either 30 min or 10 minutes (depending on +/- assessment) – total 2 hours 3. Bibliotherapy: treatment manual only – 1.5hrs of time with therapist was for assessment only.	UK primary care – Scotland!	132 referred 104 satisfied entry criteria 13 dropped out 91 completers n.b. completers included those who dropped out because of treatment effectiveness or ineffectiveness or those who had more than 42 days treatment. Std therapy: 30 completers, 1 defined completer Min therapy: 30 completers, 1 defined completer Bibliotherapy: 29 completers 10 defined completers	<u>Inclusion criteria</u> DSM III R Min 15 HAM Anx scale Max 20 Mont Asb scale Symptoms for <3 months 18 - 70 yrs No psych treat for PD received in 6 months prior to treatment Patients continued to take psychotropic medication if they had been taking it for longer than 2 months prior to the study.	No statistical difference between treatment groups at entry No statistical differences in proportion of patients taking psychotropic medication at entry	Intervention lasted 84 days No longer term follow up	Severity of illness: Global symptom severity scale 1 – 7 <i>Scales assigned by therapeutic therapist at day 0 and by assessment therapist at day 84 – why was it different?</i> Change in symptoms: Clinical global improvement scale 1 – 7 <i>Scales assigned by therapeutic therapist at day 0 and by patients at day 84</i> Social function: Sheehan patient rated at Days 0 and 84 Scheffe post hoc tests used to detect between group differences

Results

Severity of Symptoms:

No sig. differences between groups at Day 0

Std treatment sig. better than min treatment or bibliotherapy at Day 84 (One way ANOVA, Two tailed *t-test*) $p = <0.0001$

No difference between min treatment or bibliotherapy at Day 84 ($p = 0.05$)

Std treatment and min treatment likely to be effective ($p=0.0001$); bibliotherapy less likely to be effective ($p = 0.05$)

Change in Symptoms:

Considerable correlation between therapist rating and patient rating (Pearson coefficient of correlation $r= 0.86 P<0.001$)

Treatment with a psychologist therapist showed sig. greater changes in symptoms than bibliotherapy. True for both patient assessment and for therapist assessment.

Sheehan Disability Scale

Std treatment showed sig. lower ratings post treatment in disruption to employment than either of the other two groups (which showed no difference between themselves)

Std and min treatment showed sig. lower ratings post treatment in disruption to social life and disruption to home life than bibliotherapy.

All groups showed reduction in scores pre – post treatment on disruption to social life, and std and min therapist treatments showed sig. reduction in ratings on disruption to work and home life.

The Message(s)

1. Std treatment here (6 hrs) is brief by anybody else's assessment!
2. Bibliotherapy in this study showed weakest treatment response, min treatment showed an intermediate treatment response, and std treatment showed the most comprehensive treatment response
3. The authors believe that since the results show this disparity, it supports their contention that the scales proposed here, can be used as outcome measures

Unanswered Questions:

1. was the overall outcome of this std (in fact brief) treatment as good as treatment responses for longer therapeutic interventions for CBT ?
2. I think the study shows that that patients get better if they are spoken to by a person!

RCT extraction table

Author (s)	Study (Type of intervention (pharmacotherapy & name of therapy) Length of study	Setting and location (primary/sec ondary care or other & country)	Numbers randomised Randomisation method Numbers incl in results analysis (Confirm ITT analysis or % included in results)	Inclusion criteria/ Exclusion criteria Exclusion of depression Permitted polypharmacy Washout period Substance misuse Concordance (compliance)	Mean age (years) Male/female (M/F) ratio Ethnicity	Follow-up period	Main outcome measures (extract data on primary outcome measure only and just note secondary outcome)
Power, K. G., Sharp, D. M., Swanson, V., & Simpson, R. J. 2000, "Therapist contact in cognitive behaviour therapy for panic disorder and agoraphobia in primary care", <i>Clinical Psychology & Psychotherapy</i> , vol. 7, no. 1, pp. 37-46.	RCT	3 groups 1. CBT with 'standard' therapist contact (8 sessions of 45 minutes each over 12wks= total of 6 hours therapist contact) 2. CBT with 'minimum' therapist contact (6 sessions involving assessments of 30 minutes each and 3 sessionsx10 minutes over 12 weeks = total of 2 hours therapist contact) 3. Bibliotherapy(3 sessions for assessment only over 12 weeks a total of 1.5 hours therapist contact) CBT patients all were seen by the same therapist and received the same instructions and treatment CBT emphasised both gross exposure and behavioural and cognitive panic management techniques. Pragmatic design	UK Primary Care - Local GP surgery or health centre	N=104 13 dropped out during the study period 'Patients who failed to complete the entire study period having withdrawn due to early effectiveness or ineffectiveness who received at least 42 days of treatment and who provided adequate end-point data were included in the final analysis as 'defined completers' = 'modified' ITT	Inclusion: PD with or without agoraphobia - DSM III-R Score GE 15 on HAM-A Score LE 20 Montgomery Asberg Depression Scale Symptoms of at least 3 months Age 18-70 No psychological treatment for PD for at least 6 months prior to entry. Patients were not concluded for taking concurrent psychotropic medication but were required to continue taking it during the study period.	Mean age =35 Ethnicity and M/F ratio not given. There were no significant differences on demographic or clinical measures between groups at entry	6 months post treatment	Assessments were made at day 0, day 42, day 84 and 6 months post treatment Anxiety measures o Psychologist rated HAM-A o Patient Rated SRT Depression Measures o MADRS Agoraphobia o Agoraphobia subscale of the Fear Questionnaire Panic Attacks prospectively recorded in patient diary. Analysed as proportion of patients free from major attacks at treatment endpoint o

Results: treatment, comparator data, dropouts (numbers/percentage and reasons), treatment emergent adverse events (whether spontaneous report or questioned by researcher/treating clinician), investigator's conclusions and reviewers conclusions if different from investigators

Post treatment the 'standard' and minimum therapist contact groups showed significant reductions on all measures. At post treatment, the minimum contact group had produced results which were statistically equivalent to the standard treatment group. However, when determined by clinical significance, the differences between the standard and minimum contact groups were significant for the proportion of patients achieving clinically significant change dor the MADRS and the Advanced criterion HAM-A. Results of clinically significant change at post treatment and at 6 months are in the in table below.

Table 4. Number (%) of patients in each group achieving clinically significant change on HAM-A, SRT, FQ-AG and MADRS at day 84

<i>Day 84</i>	<i>Standard</i>	<i>Minimum</i>	<i>Bibliotherapy</i>
HAM-A	26 (83.8%)	21 (67.7%)	10 (34.5%)
SRT	18 (58.1%)	11 (35.5%)	4 (13.8%)
FQ-AG	26 (83.8%)	23 (74.2%)	17 (58.6%)
MADRS	18 (58.1%)	10 (32.2%)	5 (17.2%)
Advanced Criterion HAM-A	24 (77.4%)	14 (45.1%)	8 (27.5%)

Table 5. Number (%) of patients in each group with no intervening psychological treatment who continue to achieve clinically significant change on HAM-A, SRT, MADRS and FQ-AG at 6-month follow-up

<i>6-month follow-up</i>	<i>Standard</i>	<i>Minimum</i>	<i>Bibliotherapy</i>
HAM-A	19 (61.3%)	7 (22.6%)	7 (24.1%)
SRT	13 (41.9%)	9 (29.1%)	4 (13.8%)
MADRS	14 (45.2%)	8 (25.8%)	5 (17.2%)
FQ-AG	17 (54.8%)	14 (45.2%)	6 (20.7%)
Advanced Criterion HAM-A	18 (58.1%)	5 (16.1%)	7 (24.1%)

Author (s)	Study Design	Comparisons	Setting and location	Numbers of participants	Inclusion criteria/ Exclusion criteria	Characteristics of participants	Follow-up period	Main outcome measures Analysis
Clark et al Brief CBT for PD – a RCT. J Consulting and Clinical Psychology, 1999	RCT comparing Full CBT (FCBT) against brief CBT (BCBT) against a control of sitting on the waiting list for treatment	FCBT vs BCBT vs waiting list	UK psychology OPD	43	<u>Inclusion Criteria</u> DSM III R Duration at least 6 months At least 3 P.A.s in the 3 weeks preceding the study PD is the main problem 18 – 60 Willingness to be randomised No depressive disorder severe enough to require immediate treatment (?) Not on psychotropic meds – or on stable dose and agreement not to change the dose No evidence of organics brain disorder, schizophrenia Record of at least one P.A. while keeping a post interview 2 week baseline period	Mean age 34 Duration of PD 3.7 years 62% female 32% were on stable medication No sig. differences in any group	Study lasted 12 weeks with follow up at 3 months and at 12 months	<u>Outcome measures:</u> Patient scored panic frequency Assessor scored panic frequency Patient scored panic related distress Assessor scored panic related distress Beck Anxiety Patient scored general tension Assessor scored general tension Agoraphobic avoidance BBSIQ ACQ frequency ACQ Belief Beck depression 2 step approach used by creating a panic – anxiety composite measure – if this measure revealed significant between group differences individual panic anxiety measures were analysed

Results

Did it work?

Patients thought both interventions (full and brief) CBT logical and would recommend it to a friend
Pre treatment: there was no significant difference between either treatment group and control (wait list) group
Post treatment there was a significant difference between both intervention groups and control (wait list) group. (p = 0.005)
There was no significant difference between either intervention group
The authors conclude that BCBT is as effective as FCBT

Did it last?

Evaluation at 3 and 12 months showed that there was no difference between BCBT and FCBT, and that the gains made in treatment were maintained. *From the table or results, it would appear that 79% BCBT and 71% of FCBT were better at 12 months – but the n is small only 14, and it does not explain why brief CBT apparently lasted better (???) than FCBT – maybe the differences are not significant?*

The authors undertook a number of additional analyses to check possible confounding features, alternative interpretations – they believe that the statistics support their view that BCBT is as good as FCBT

Will it work in “real life”?

The authors correctly point out that the intervention was provided by experienced therapists – they are unsure if the results can be transported to “real life”

Treatment and compliance

Cohort Studies

Author (s)	Study Design	Comparisons	Setting and location	Numbers of participants	Inclusion criteria/ Exclusion criteria	Characteristics of participants	Follo w-up period	Main outcome measures Analysis
Schmidt, N. B. & Woolaway-Bickel, K. 2000, "The effects of treatment compliance on outcome in cognitive-behavioral therapy for panic disorder: Quality versus quantity", Journal of Consulting and Clinical Psychology, vol. 68, no. 1, pp. 13-18.	<p>Compliance CBT in PD on outcome using both quality and quantity of homework as a marker of compliance.</p> <p>Consecutive patients presenting to clinic who fulfilled the inclusion criteria received group administer CBT for PD of 12 sessions x 12 weeks.</p> <p>Treatment included:</p> <ul style="list-style-type: none"> • Education • Cognitive restructuring • Interoceptive exposure • In vivo exposure <p>Patients were assigned a number of homebased assignments following each session.</p>	CBT	Home based - USA	<p>N=48</p> <p>38/48 patients were assessed at post treatment</p> <p>Comparisons between completers and drop-outs showed not significant differences.</p>	<p>Inclusion</p> <ol style="list-style-type: none"> 1. Axis I diagnosis of PD with or without agoraphobia (DSM-IV) 2. No change in medication type or dose for 12 weeks before treatment <p>Exclusion</p> <ol style="list-style-type: none"> 1. Evidence of suicidal intent or substance abuse 2. Current or past history of schizophrenia, BPD or organic mental disorder <p>52% were taking psychotropic medication</p>	<p>Mean age = 35 years</p> <p>Female 66%</p> <p>Caucasian = 86%</p>		<p>Clinician rated measures of</p> <ul style="list-style-type: none"> ▪ Panic frequency ▪ Intensity ▪ Anticipatory anxiety ▪ Impairment (MC=PAS) ▪ Quality and Quantity of homework <p>Self-rated</p> <ul style="list-style-type: none"> ▪ Sheehan patient rated anxiety scale (SPRAS) ▪ Mobility inventory for agoraphobia Alone and accompanied (MI) ▪ Sheehan Disability Scale (SDS) ▪ Estimates of time spent on homework <p>Quantity and Quality Compliance of homework rating by independent assessment</p> <p>End-state functioning</p> <p>'Recovered' defined as scores on 3 dimensions were in the normal range (panic frequency =0, SPRAS <30 and MI alone <1.5)</p>

Results

Compliance ratings

Patients reported working an average of 3 hr/wk and 3 days/wk. Therapists rated patients as completing an average of 60% of assignments. Quality rates were largely in the 'good' range but improved with time.

Relationship between demographic variables and compliance

There were significantly positive correlations between quality compliance rating and age and employment status (older and unemployed people tended to have better quality work)

Medication status was not correlated with quality

Response to treatment

Paired t-tests showed significant improvement on all measures at post treatment. The recovery rate was 94% of panic attacks, 83% for anxiety and 71% for phobic avoidance.

63% were recovered on all three measures.

Relationship between compliance and outcome

Using step-wise multiple regression, patient rating of compliance showed no relationship to outcome. Therapist rating of compliance was consistently and significantly related to clinical improvement with quality ratings being better predictors of outcome than quantity although the two were strongly correlated.

Independent assessor was similar to therapies with quality ratings being a better predictor.

Effects of individual session quality of compliance on outcome

Using regression analysis, indicated that compliance with particular skills was associated with improvement in that symptom variable.

Moderator Analysis

No indication of moderator effects.

Authors Conclusions

As quality of homework is a predictor of outcome therapists may want to pay attention to the detail of what constitutes good work and to devote sufficient time training patients how to do homework. Discusses these as markers for motivation.

Therapist variables

Author (s)	Study Design	Comparisons	Setting and location	Numbers of participants	Inclusion criteria/ Exclusion criteria	Characteristics of participants	Follow-up period	Main outcome measures Analysis
Huppert, J. D., Bufka, L. F., Barlow, D. H., Gorman, J. M., Shear, M. K., & Woods, S. W. 2001, "Therapists, therapist variables, and cognitive-behavioral therapy outcome in a multicenter trial for panic disorder", Journal of Consulting and Clinical Psychology, vol. 69, no. 5, pp. 747-755	Original RCT with placebo and active comparator with complementary study to determine whether particular therapists have better outcomes overall or with specific patient populations or disorders. Patients were randomly assigned to 1 of 5 groups for treatment <ul style="list-style-type: none"> • CBT only • CBT + Placebo • CBT + Imipramine • Imipramine • Placebo <p>Results reported in Barlow et al 2000 this study used this patient population.</p> <p>For this study grouped as:</p> <ul style="list-style-type: none"> • CBT (CBT only, CBT + Placebo and CBT + Imipramine) 	Examined the relationship of age, gender, treatment orientation, experience and specific experience with CBT to treatment outcome.	Multi-centre in USA	Therapists = n=14	No information how patients were allocated to therapists.	(7=female) 13 were psychologists and one a psychiatrist. Mean age = 35.7 years Experience in general psychotherapy ranged from 2-20 years mean=8.9 Experience in CBT ranged from 1-18 years mean=5.9 Nine described their orientation as primarily CBT.	N/A	Patient Outcomes Adherence Competency
<p>Results: treatment, comparator data, dropouts (numbers/percentage and reasons), treatment emergent adverse events (whether spontaneous report or questioned by researcher/treating clinician), investigator's conclusions and reviewers conclusions if different from investigators</p> <p>A 'therapist effect size' was calculated.</p> <p>Therapists with more experience in therapy in general were more likely to have patients' anxiety sensitivity decrease. Older therapists and those with more experience were associated with more change in overall panic disorder severity. As rated on the ADIS-R. No differences in outcome were found when examining the effects of therapist patient match or mismatch for gender.</p> <p>The 14 therapists were divided into 3 groups on the basis of treatment outcome not used in the results analysis. 6 were 'above average', 4 were average and 4 were below average.</p> <p>Above Average Therapists differed significantly from below average therapists in the average amount of change experience by their patients. Below average therapists were more likely to have patients that did not qualify as responders. These differences were attributable to above average therapists' patients:</p> <ul style="list-style-type: none"> • Being less likely to be non-responders • Having greater improvement if they did respond to treatment <p>There was no difference in patient adherence between 3 groups of therapists nor in treatment assignments nor between centres.</p>								

Allocation by preference

Author (s)	Study (placebo controlled, active comparator etc.)	Type of intervention Length of study	Setting and location	Numbers randomised	Inclusion criteria/ Exclusion criteria Exclusion of depression Permitted polypharmacy	Mean age (years) Male/female (M/F) ratio Ethnicity	Follow-up period	Main outcome measures (extract data on primary outcome measure only and just note secondary outcome)
Bakker, A., Spinhoven, P., van Balkom, A. J., Vleugel, L., & van Dyck, R. 2000, "Cognitive therapy by allocation versus cognitive therapy by preference in the treatment of panic disorder", <i>Psychotherapy & Psychosomatics</i> , vol. 69, no. 5, pp. 240-243.	Investigation of possible differences in outcome between PD patients with preferred CT and those treated by randomisation for same intervention 35 treated by random allocation in another 3 armed study of the efficacy of paroxetine, clomipramine and CT and 31 patients who refused to be randomized and were treated by preference with CT.	3 week attention placebo pre-treatment followed by 12X 45 minute weekly sessions.	Outpatient clinic for anxiety disorders in Amsterdam.	N=66 Analysis of completers and ITT	Inclusion: <ul style="list-style-type: none"> At least 3 panic attacks during 3 week attention placebo phase 18-70 years 'PA' as main diagnosis on DSM-II-R criteria 	Female (74%) Mean age 33.9 years Mean Duration of complaints 7.3 years	None	Panic frequency from panic diaries CGI-S Patient Global Evaluation HAM-A Marks-Sheehan Phobia Scale (MSPS) Sheehan Disability Scale (SDS) Agoraphobic Cognition Questionnaire (ACQ) Bodily Sensations Questionnaire (BSQ) Montgomery-Asberg Depression Rating Scale (MADRS)
<p>Results</p> <p>Dropouts 9/33 randomised group 7/31 preference group Dropouts may have had more severe depressive symptomology</p> <p>Number of panic free patients Randomised Group =14 (54%) Preference Group = 12 (50%) ns</p> <p>Authors Conclusion: Preference for type of treatment is not a powerful moderator effect.</p>								

Location of treatment

Author (s)	Study Design	Comparisons	Setting and location	Numbers of participants	Inclusion criteria/ Exclusion criteria	Characteristics of participants	Follow-up period	Main outcome measures Analysis
12734 Stuart, Treat & Wade Effectiveness of an empirically based treatment for panic disorder delivered in a service clinic setting: 1-year follow-up In <i>Journal of Consulting and Clinical Psychology</i> 2000, Vol 68, No. 3, 506-512	Quasi-experimental – cohort	With non-completers studies of efficacy	Community Mental Health Centre in the United States	81 (completers) 29 (noncompleters)	Include: Patients with a diagnosis of Panic Disorder with or without agoraphobia re DSM-III-R Exclude: Active symptoms of alcohol or drug dependency, psychosis, or mental disorder due to a medical condition. There was no exclusion on the basis of medication use or changes, severity or frequency of panic attacks, age, or the presence or severity of agoraphobia.	Clients who received CBT for panic disorder at eh Center for Behavioral Health in Bloomington, Indiana	1 Year	Fear Questionnaire (FQ) Beck Depression Inventory (BDI), the positive and negative affect schedule (PANAS)

Results

The study methodology says that it intends to examine differences between completers and non-completers and nothing in the table of presented results gives that information. Perhaps that is done in the original study. There were few differences between former participants who had been contacted and those that had not. Contact clients were more likely to be married, endorsed less agoraphobia on the Fear Questionnaire and less interference of agoraphobia in their lives at pre-treatment, and reported significantly higher self-monitored depression at post-treatment.

Comparison from pre-treatment to 1-year follow-up (with pre-treatment to follow up in benchmarking studies): CMHC clients improved significantly on all measures at follow-up.

Comparison from post-treatment to 1-year follow-up (with post-treatment to follow up in benchmarking studies): Improvement attained at post-treatment was maintained and in some cases improved at follow-up.

Samples scoring in the normative range of functioning at pre-treatment, post-treatment, and follow-up

Variable	Criterion for recovery	CMHC			Barlow et al (1989)/ Craske et al (1991)			Telch et al (1993)		
		Pre	Post	FU	Pre	Post	FU	Pre	Post	FU
Panic Attacks	Panic attacks =0	32	88	89	15	85	87	29	85	83
	Anticipatory anxiety score <2		25	79						
	ASI<27							32	97	87
Avoidance	FA-Ag < 12	46	66	72				62	85	90
Depression	BDI < 10	30	73	75				24	65	60

NOTE: Empty cells indicate that the information was not reported.

Investigator's conclusions: **Despite differences in settings, clients, and treatment providers, both the magnitude of change from pre-treatment to follow-up and the maintenance of change from post-treatment to follow-up in the CMHC sample were comparable with the parallel findings in the efficacy studies. At follow-up 89% of the CMHC client were panic free and a substantial proportion of the sample successfully discontinued benzodiazepine use.**

Reviewers note: **It is assumed, although not stated that the 89% of panic free patients are 89% of the contactable clients at follow-up, thus providing a more conservative result.**

Table 2. Characteristics of Clients in Community Mental Health Center (CMHC), Barlow et al. (1989)/Craske et al. (1991), and Telch et al. (1993) Samples Who Received Similar Treatment

	CMHC*			Barlow et al. (1989)/Craske et al. (1991)			Telch et al. (1993)		
	Pre	Post	FU	Pre	Post	FU	Pre	Post	FU

Variable	(n = 110)			(n = 81)			(N = 57)			Pre vs. FU	Post vs. FU	(n = 15)			(n = 15)			(n = 15)			(n = 34)			(n = 34)			(n = 30)		
	M	SD	%	M	SD	%	M	SD	%			M	SD	%	M	SD	%	M	SD	%	M	SD	%	M	SD	%	M	SD	%
% panic free			32			88			89						15			85			87			29			85		
No. of panic attacks in past week	2.0	2.4		0.2	0.5		0.2	0.7		/(52)= -5.82***	/(54)= -0.23	1.2	1.0		0.7	1.7		0.4	1.1		4.2	9.5		0.2	0.5		0.5	1.3	
Anticipatory anxiety	3.4	1.5		1.6	1.3		1.1	1.4		/(44)= -7.28***	/(38)= -1.45																		
General anxiety	3.5	1.4		2.4	1.2		2.1	1.7		/(47)= -4.73***	/(38)= -0.23	1.9	1.0		1.2	0.8		0.6	0.4										
Depression	2.3	1.7		1.5	1.6		1.6	2.1		/(39)= -1.63	/(36)= 0.72	1.7	0.8		1.2	1.0		0.6	0.7										
Fear Questionnaire																													
Agoraphobia	15.1	11.4		8.9	7.5		7.4	7.4		/(53)= -5.61***	/(40)= -0.86										12.2	11.4		5.1	6.8		5.6	7.9	
Blood Injury	13.5	8.6		11.3	7.7		8.1	6.2		/(53)= -4.36***	/(40)= -2.30*																		
Social Phobia	16.0	9.0		9.9	7.2		8.1	6.3		/(53)= -6.00***	/(40)= -1.39																		
BDI	14.4	7.8		6.5	6.4		5.3	6.9		/(50)= -6.64***	/(36)= -1.18	13.5	8.9		12.4	7.4		7.7	5.8		16.9	8.2		7.7	5.3		7.7	6.7	
PANAS																													
Positive Affect	25.9	7.9		32.5	8.3		36.3	8.1		/(54)= -7.58***	/(40)= 3.15**																		
Negative Affect	30.5	8.8		17.5	6.9		18.2	5.7		/(54)= -8.35***	/(40)= 0.63																		
Anxiolytic medication			63			23			27					40		13								47					
Benzodiazepine for anxiety			55			20			18				41 ^b		24 ^b		22 ^b												
Medication other than benzodiazepine for anxiety			16			7			9																				
Depression medication			19			16			20				6 ^b		2 ^b		8 ^b						12						

Note. Empty cells indicate that the information was not reported. Pre = pretreatment; Post = posttreatment; FU = follow-up (1 year for the CMHC sample, 2 years for the Barlow et al., 1989/Craske et al. 1991, sample, and 6 months for the Telch et al., 1993 sample); BDI = Beck Depression Inventory; PANAS = Positive and Negative Affect Schedule. *Because of missing data, the sample sizes varied on each measure. ^bThese data were reported in the study by Brown and Barlow (1995), derived from a larger sample that included the original 15 participants. *p<.05. **p<.01. ***p<.001.

Exposure Therapy

Matched pair study

Author (s)	Study Design	Comparisons	Setting and location	Numbers of participants	Inclusion criteria/ Exclusion criteria	Characteristics of participants	Follow-up period	Main outcome measures Analysis
Fava et al Psych medicine 2001	Long term FU of 200 patients , treated by exposure technique for PDwA	n/a	Consecutive 200 patients treated at Bologna OP programme over 12 year period <i>Not very many people – we see that many in two weeks!</i>	200 132 were followed up No reason given for the 68 pts not followed up – and all results are based on the 132 not the 200 who entered the study.	<u>Inclusion</u> DSM IV PD with agoraphobia <u>Exclusion</u> DSM IV depression co-occurring social phobia OCD	Age: 34.5 (8.8) SD Sex m/f 35/97 Marital status 82 married At least 13 yrs education 88 of 132 90/132 were middle class 96 of 132 had no Axis 1 co-morbidity 116 of 132 had no axis 2 co-morbidity 102 of 132 had not used anti-depressants 93 of 132 had not used benzo.s 86 of 132 were working outside the home	2 – 14 years (median 8 yrs)	Annual FU since treatment Review of progress/relapse in previous year Clinical Interview for Depression Possible predictors investigated included: Age, gender, social class, marital status, social class, level of education, employment, duration of illness, presence of an additional psychiatric diagnosis, presence of personality disorder, initial levels of panic, and the use of medication

Results

All of the 132 patients accepted follow up assessments; otherwise they would have been excluded from the results analysis. See “setting” above
The analysis of the statistics should therefore be treated with a little caution

Cumulative percentage of patients remaining in remission after treatment was

93.1% 2 years after completing treatment,

82.4% after 5 years

78.8% after 7 years

62.1% after 10 years

31 patients relapsed, and were offered a further course of treatment

28 became panic free

6 patients had a second relapse

2 patients had a third relapse

Predictors for outcome:

Personality disorder associated with worse prognosis $p=0.001$

Pre treatment level of depression associated with relapse in first 2 years $p=0.05$

Overcoming agoraphobic avoidance behaviour associated with a better outcome $p=0.05$

Patients who were still taking benzo.s at the end of the exposure treatment had worse outcome those who were drug free $p=0.05$

Patients who were using anti-depressants prior to treatment had worse outcome than patients who were drug free $p=0.05$

Younger patients had a better outcome than older patients $p=0.05$

The message

Despite some methodological problems, it seems that exposure technique provides long term remission from PD with agoraphobia

The paper identifies some interesting predictors of outcome

Author (s)	Study Design	Comparisons	Setting and location	Numbers of participants	Inclusion criteria/ Exclusion criteria	Characteristics of participants	Follow-up period	Main outcome measures Analysis
Fava et al Psychological well being and residual symptoms is PDwA	30 patients were treated for PDwA by standard exposure technique and got better – were compared to 30 normal subjects	30 matched controls	Bologna OPD	30 + 30 controls	<u>Inclusion</u> DSM IV No co-morbidity on axis 1 or 2 No active medical illness Successful response to treatment	Mean age of 31.0 (sd -5.9) 25 of 30 were women 14 of the 30 were married 22 of the 30 were “middle-upper” class	n/a	Paykels Clinical Interview for Depression Scale for Personality Disturbances Scale of Psychological Wellbeing Symptom Questionnaire

Results

Remitted patients with PDwA showed considerably greater psychological distress than the age/sex matched controls

Greater psychological distress measured by an observer rated scales, or by self rated scales confirm when combined a highly significant difference between the intervention group (those who had remitted) and the control group $p=0.001$

Definition of remission used in the paper: Kellner (1972) global scale of improvement – doesn't say what this is, just quotes the paper.

The Message

If the methodology is accepted, then exposure technique may cause an improvement in the number of panic attacks, but there are still significant psychological symptoms that are not resolved and will interfere with quality of life.

If the methodology is questioned:

What is the definition of remission used

How long were the patients followed up for?

Why use a 92 question self rated questionnaire where each question is rated from 0 – 17?!

Internal/external cues

RCT extraction table

Author (s)	Study (placebo controlled, active comparator etc.)	Type of intervention (pharmacotherapy & name of therapy) Length of study	Setting and location (primary/secondary care or other & country)	Numbers randomised Randomisation method Numbers incl in results analysis (Confirm ITT analysis or % included in results)	Inclusion criteria/ Exclusion criteria Exclusion of depression Permitted polycharmacy Washout period Substance misuse Concordance (compliance)	Mean age (years) Male/female (M/F) ratio Ethnicity	Follow-up period	Main outcome measures (extract data on primary outcome measure only and just note secondary outcome)
Ito et al B J Psych 2001	RCT of external cues, vs. Internal cues vs. Combined external and internal cues vs. control	Psychological, self exposure to different types of cues to reduce avoidance behaviour in PD	Portuguese OPD Patients were self referred following an advert in lay press	90 patients met inclusion criteria and were offered treatment 20 did not return 70 started treatment The initial 20 were replaced by new patients, hence the number of patients in the study was 80. Confused?	<u>Inclusion</u> DSM IV for 1 year 18 – 65 years of age Absence of suicidal intent, organic brain disease, past or present psychosis, psychotropic medication, or excess alcohol, no response to exposure in the last two years, no other current psychotherapy	51/80 were female Age 37 (sd= 11) Mean age of onset 29 (sd =10) Illness duration (7 sd = 8)	Treatment period 0 – 10 weeks Follow up 10 – 62 weeks	Two phobic targets (Marks and Gelder) Four work/social adjustment items (Marks) Self rating scales FQT Agoraphobic Cognitions Questionnaire BDI Assessor rating scales HAS CGI

Results: treatment, comparator data, dropouts (numbers/percentage and reasons), treatment emergent adverse events (whether spontaneous report or questioned by researcher/treating clinician), investigator's conclusions and reviewers conclusions if different from investigators

Improvement during Treatment

All intervention groups, either external cues, internal cues, or both, were individually and combined were effective at treating the symptoms of PD.
Effect sizes were large for all three groups (E 2.5; I 3; E+I 1.6)

Follow up after treatment

52 patients were followed up
The three self exposure groups did not differ between themselves on any of the main outcome measures at 62 weeks
Effect sizes increased after 1 year:
Phobic target avoidance (E 4.7; I 3.5; E+I 3.8)
CGI (E 4.1; I 3.3; E + I 4.3)
HAS (E 2.8; I 3.5; E+I 3.4)

The message

Any of the self exposure techniques seem equally effective, and much more so than a control group.
Combining external and internal techniques are not synergistic
The authors believe that self exposure to external stimuli is easier to administer (but not nearly as much fun!)

EMDR

RCT extraction table

Author (s)	Study (placebo controlled, active comparator or etc.)	Type of intervention (pharmacotherapy & name of therapy) Length of study	Setting and location (primary/secondary care or other & country)	Numbers randomised Randomisation method Numbers incl in results analysis (Confirm ITT analysis or % included in results)	Inclusion criteria/ Exclusion criteria Exclusion of depression Permitted polypharmacy Washout period Substance misuse Concordance (compliance)	Mean age (years) Male/female (M/F) ratio Ethnicity	Follow-up period	Main outcome measures (extract data on primary outcome measure only and just note secondary outcome)
Goldstein AJ, de Beurs E, Chambless DL, Wilson KA. , 2000, EMDR for Panic Disorder with agoraphobia: Comparison with Waiting list and credible attention-placebo control conditions J Consult Clin Psychol 2000 Dec;68(6):947-56	Both waiting list and credible attention-placebo control groups. Attention-placebo group received the same amount of therapist contact as EMDR	Eye movement desensitization and reprocessing (EMDR) – a technique mainly used with PTSD – in this study being tested for PD. 6x90 minute sessions heal over an average of 4 weeks. EMDR was delivered according to the manual. ART (a Association and Relaxation therapy) was the attention-placebo, consisted of 30-45 minutes of progressive muscle relaxation training and 45-60 minutes of association therapy	USA – two clinics in PA and NC	Waiting List n=14 EMDR n=18 Attention-placebo n=13 Once waiting list ended group was randomised to: EMDR n=6 Attention-placebo n=7 Follow-up was 1 month posttest Therapists were crossed with treatment condition and were randomly assigned clients within scheduling constraints. Dropouts were replaced with the next participant to enter the study. 4/46 dropped out 5/42 failed to provide follow up data Intention to treat analyses were conducted at each assessment period by repeating ANOVAs and ANCOVAs with pretest scores carried forward.	Met DSM-IV criteria for PDA of at least 1 year duration with agoraphobia avoidance severity of moderate for 6 months. Age 18-65 Exclusion – <ul style="list-style-type: none"> in therapy elsewhere and not willing to suspend. Dosages of alprazolam GT 1.5 mg p.d or similar benzo. Taken anti-depressant or anti-anxiety medication for LT 6 months or changed in the last 12 weeks. Major psychiatric disorder (listed) 	Mean age = 38.16 Female n=37 Caucasian except 3 20 had at least one Axis I co-morbid condition (listed and detailed) The ART group had longer duration of panic compared to EMDR group but this was factored into co-variant analysis		<u>Self report and interview measures</u> <ul style="list-style-type: none"> – Agoraphobic Cognitions Questionnaire – Body Sensations Questionnaire – 7 panic related items of the Brief Body Sensations Interpretation Questionnaire – Panic Appraisal Inventory – Mobility Inventory – Beck Depression Inventory – Beck Anxiety Inventory – Brief Symptom Inventory – Adapted Distress Questionnaire – Panic Disorder Severity Interview Self monitoring forms Treatment Expectancy Scale Therapist rating scale

Results: treatment, comparator data, dropouts (numbers/percentage and reasons), treatment emergent adverse events (whether spontaneous report or questioned by researcher/treating clinician), investigator's conclusions and reviewers conclusions if different from investigators

Repeated measures of ANOVA's and ANCOVA,s showed that EMDR was significantly superior to waiting list on panic/agoraphobia severity and the diary factor, but not on the cognitive factor controlling for pre-test panic frequency nor on number of panic attacks.

There were no significant difference in outcome measures between EMDR and ART

Author's conclusion: EMDR was significantly better than waiting list for some outcome measures (questionnaire, diary, and interview measures of severity of anxiety, panic disorder, and agoraphobia) but not for others (panic attack frequency and anxious cognitions). However, low power and, for panic frequency, floor effects may account for these negative results. Differences between EMDR and the attention-placebo control condition were not statistically significant on any measure, and, in this case, the effect sizes were generally small ($\eta^2 = .00-.06$), suggesting the poor results for EMDR were not due to lack of power. Because there are established effective treatments such as cognitive-behavior therapy for PDA, these data, unless contradicted by future research, indicate EMDR should not be the first-line treatment for this disorder.

Psychoanalytic therapy

Author (s)	Study Design	Comparisons	Setting and location	Numbers of participants	Inclusion criteria/ Exclusion criteria	Characteristics of participants	Follow-up period	Main outcome measures Analysis
Milrod, B., Busch, F., Leon, A. C., Aronson, A., Roiphe, J., Rudden, M., Singer, M., Shapiro, T., Goldman, H., Richter, D., & Shear, M. K. 2001, "A pilot open trial of brief psychodynamic psychotherapy for panic disorder", <i>Journal of Psychotherapy Practice & Research</i> , vol. 10, no. 4, pp. 239-245.	<p>Pilot open trial to estimate the magnitude of change over the course of treatment.</p> <p>It consisted of twice-weekly, 24-session treatments of 45 minutes manualized psychodynamic psychotherapy -, Panic-Focused Psychodynamic Psychotherapy (PFPP) following PFPP treatment manual.</p>	<p>No placebo or comparators.</p> <p>Before and After with ITT using LOCF</p>	USA	21 patients started and 4 dropped out during treatment	<p>Inclusion –</p> <ul style="list-style-type: none"> • 18-50 • DSM-IV for PD (ADIS) primary diagnosis • No other form of psychiatric treatment • Agree Discontinue psychotropic medication use during treatment and follow-up period. • Medication free for 4 weeks prior to starting 3 week panic diary. • DSM-IV for criteria PD with or without agoraphobia. • At least one attack per week for the month prior to study entry <p>Exclusion</p> <ul style="list-style-type: none"> • Medication • Substance abuse • Active major depression • Lifetime history of mania, schizophrenia, delirium or dementia 	<p>66% female</p> <p>19% black</p> <p>Mean age 32</p> <p>76% had primary diagnosis of PD with agoraphobia</p> <p>24% had primary diagnosis of PD without agoraphobia</p>	Termination of treatment and at 6 months	<p>ADIS</p> <p>Anxiety Sensitivity Inventory (ASI)</p> <p>Marks and Matthews Fear Questionnaire (FQ)</p> <p>Panic Disorder Severity Scale</p>

Results

Sixteen of 21 experienced remission of panic and agoraphobia. Improvements in symptoms and in quality of life were substantial and consistent across all measured areas. Symptomatic gains were maintained over 6 months. This report was prepared specifically to describe 6-month follow-up on these patients. Effect sizes were calculated and significant differences were found at Week 40 compared to Week 0 on BSQ, ACQ, Ham-A, FQ, PDSS and ASI

Meta analysis/systematic review extraction table

Author (s)	Research question	Review type Databases used Time period covered Data analysis	Study design Interventions Follow-up period	Numbers randomised	Total sample number Age (mean/SD/range) Male/female Ethnicity	Outcomes
Fisher & Durham 1999, Recovery rates in GAD following psychological therapy: an analysis of clinically significant change in the STAI-T across outcome studies since 1990 <i>Psych Medicine</i> , vol. 29, no. 6, pp. 1425-1434.	Recovery rates in generalized anxiety disorder following psychological therapy: an analysis of clinically significant change in the STAI-T across outcome studies since 1990. Aim as stated in the discussion, 'to reach a better understanding of the value of psychological therapy in treating a psychiatric disorder that might reasonably be said to lie at the heart of the general neurotic syndrome'	Meta-analysis of six studies Databases used: Medline, PsycLIT, Cochrane Controlled Trials Register. Time period: January 1987 to December 1998	RCTs <ul style="list-style-type: none"> • Individual Cognitive Therapy Applied relaxation • Non-directive treatment • Group cognitive therapy • Group behaviour therapy • Individual behaviour therapy • Analytical psychotherapy 	404	318 age, male/female numbers and ethnicity is not given	Clinically significant change as measured By the STAI-T according to the Jacobsonian criteria.

Results								
STAI-T outcome scores divided between pre to post treatment and pre to 6 months follow-up in percentages of:								
Worse		No Change		Improved		Recovered		
Pre to post-treatment	Pre-to 6 month follow-up	Pre to post-treatment	Pre-to 6 month follow-up	Pre to post-treatment	Pre-to 6 month follow-up	Pre to post-treatment	Pre-to 6 month follow-up	
CBT	0	32	33	15	11	53	56	
BT	6	67	53	17	21	11	13	
AR	0	50	-	33	-	17	-	
CT	0	75	-	25	-	0	-	
CT+AR	0	0	-	15	-	14	-	
Grp CBT	0	63	37	11	38	26	25	
Grp BT	0	54	29	28	38	18	33	
Grp CT	0	44	33	24	24	32	43	
Grp Placebo	0	56	33	22	22	22	33	
ND	0	44	33	38	27	19	40	
AR	0	24	13	17	6	59	81	
CBT	0	29	12	0	23	71	65	
AP low contact	7	57	85	29	0	7	7	
AP high contact	18	56	55	28	36	9	0	
CT low contact	6	31	33	25	17	38	50	
CT high contact	0	36	36	36	21	28	43	
AMT	0	50	67	25	25	25	8	
AR/SCD	0	27	15	9	35	64	50	
CT	0	23	29	27	23	50	48	
CT+AR/SCD	0	23	23	18	18	59	55	
Recovery rates by treatment approach	38	87	16	40	26	28	23	
	Individual AR	Individual CBT	Non-directive therapy	Group CBT	Group BT	Individual BT	Analytical psychotherapy	
Post-treatment recovered	63	48	19	23	19	18	9	
Recovery status maintained (A)	52	41	19	18	12	7	0	
Recovery status achieved (B)	8	10	19	15	19	4	4	
Recovered overall (A+B)	60	51	38	33	31	11	4	

Self help

RCT extraction table

Author (s)	Study (placebo controlled, active comparator etc.)	Type of intervention (pharmacotherapy & name of therapy) Length of study	Setting and location (primary/secondary care or other & country)	Numbers randomised Randomisation method Numbers incl in results analysis (Confirm ITT analysis or % included in results)	Inclusion criteria/ Exclusion criteria Exclusion of depression Permitted polypharmacy Washout period Substance misuse Concordance (compliance)	Mean age (years) Male/female (M/F) ratio Ethnicity	Follow-up period	Main outcome measures (extract data on primary outcome measure only and just note secondary outcome)
Gould, Clum & Shapiro The use of bibliotherapy in the treatment of panic: a preliminary investigation Ini <i>Behavior Therapy</i> 24, 2411-252, 1993	Active comparator and wait list controlled	Psychological therapy Length of study 2 weeks baseline assessment 4 weeks treatment 1 week post-treatment follow-up	Virginia Tech staff and students (US)	Numbers randomised Randomised method: minimisation (subjects matched on level of avoidance and then randomly assigned to one of three experimental conditions. It is not clear whether the 47 eligible were all randomised. 33 subjects were assigned to treatment	Included if: not stated but included subjects met DSM-III-R criteria for panic disorder. Excluded if: seizure disorder, kidney disease, stroke, schizophrenia, organic brain syndrome, emphysema, heart attack, or chronic hypertension. Permitted polypharmacy: medication for anxiety or depression if stabilized on the medication for at least 4 weeks and continued to have panic symptoms.	Mean age: 35.7 years (SD=10.2, range 19-59 years) Male/Female ratio: 35%/65% WL= 14.2 (2.2) BT= 14.6 (SD 1.6) ITGIC=13.9 (SD 3.1)	1 week	Pre- and post-treatment measures: Frequency and duration of their panic symptoms on Daily Panic Attack Records (DPAR; Clum, 1990); Panic cognitions (PACQ; Clum, 1990); Symptoms (PASQ; Clum, 1990) and levels of avoidance (The Mobility Inventory for Agoraphobia); Anxiety Sensitivity Index (ASI), the Beck Depression Inventory (BDI), the Likelihood of having a panic attack, thoughts during a panic attack; coping with panic attacks and a Panic Self-Efficacy Questionnaire. An Expectancy Questionnaire Weekly dependent measures: DPAR, measures to assess panic symptoms, panic cognitions and level of avoidance. All groups completed this. The BT (bibliotherapy group) completed a weekly Practice Recode wherein amount of time spent practicing specific techniques outlined in the book were recorded along with exposure to anxiety-provoking situations.

Results: treatment, comparator data, dropouts (numbers/percentage and reasons), treatment emergent adverse events (whether spontaneous report or questioned by researcher/treating clinician), investigator's conclusions and reviewers conclusions if different from investigators

Dropouts: 2: 1 from Wait List (WL) group who reported having to move to a different state to seek employment and therefore could not continue and 1 from the Bibliotherapy (BT) group, who although she had completed all the dependent measures, could not be included in the analysis because she had failed to read the book
 There were significant differences between the three treatment conditions [F(12, 46) = 3.11, p=.003]. Groups did not differ significantly at pre-treatment. Neither sex nor treatment condition revealed any differences on these measures, at pre-treatment, nor did they differ on weekly dependent measures.

Variable	Main effect for Time	Interaction of Time x Group	Notes
Pre-post dependent measures			
Increases in Self-efficacy	[F(1, 30)=20.05, p=.0001]	[F(1,30)=11.50, p=.001]	BT & ITGIC groups > self-efficacy than WL subject (p<.05) but did not differ from each other.
Coping during a panic attack	[F(1,30) = 47.14, p=.0001]	[F(1,30)=6.23, p=.006]	As above
Decreases in likelihood of panic attack	[F(1,30) = 13.33, p=.0011]	[F(1,30) = 4.1, p=.05]	Only BT subjects improved significantly more than WL (p<.05)
Decreases in thoughts during panic attack	[F(1,30) = 13.85, p=.0009]	[F(1.30) = 4.28, p=.024]	As above – Only BT etc.
Depression	[F(1,30) = 11.97, p=.0018]	None	
Anxiety Sensitivity	[F(1,30) = 7.53, p=.011]	None	
Weekly dependent measures			
Decreases in Frequency of panic attacks	[F(1,30)=14.06, p=.0008]		May be related to the high (2.02) coefficient of variation for this measure across groups
Decreases in average severity of attacks	[F(1,30) = 28.09, p=.0001]	None	
Decreases in Limited-Symptom attacks	Nonsignificant		
Panic Attack Symptoms	[F(1,30)=63.26, p=.0001]	[F(1,30) = 4.12, p=.027]	At post-treatment only BT different from WL (p<.05)
Panic Attack Cognitions	[F(1,30)=97.27, p=.0001]	[F(1.30) = 5.79, p=.008]	At post-treatment both ITGIC and BT significantly difference from WL (p<.05)
Decreases in Avoidance Behaviour	[F(1,30)=14.93, p=.0006]	[F(1,30)=2.86, p=.074] (nonsignificant)	

Regression analysis revealed that amount of practice of panic reduction strategies did not predict the frequency of panic attacks reported by subjects in either the BT or the ITGIC groups

Clinical improvement, defined as either a 50% reduction in number of panic attacks, panic symptoms and panic cognitions at the end of treatment or being panic free: 4/11 in WL, 8/11 in BT, 6/9 in ITGIC. BT and WL conditions differed significantly (pair-wise comparison $z=1.76$, $p=0.05$). ITGIC and WL did not differ. There was no association with treatment expectation or therapist assignment.

73% of BT subjects panic free at the end of the study and 75% showed a 50% reduction in panic frequency, panic cognitions, and panic symptoms. Regarding anxiety sensitivity, there was no significant differences between the treatment and wait-list control groups in frequency and average severity of panic attacks.

The authors conclude that the results support bibliotherapy as a treatment approach for panic-disordered individuals who are mildly agoraphobic. The methodology is stronger than previous studies of its kind in that it measures the results of a bibliotherapy group against both a wait-list control group and a known effective therapy.

Conclusion: Subjects in the BT group were significantly more improved than subjects in WL and not significantly different from those in ITGIC.

Table 1. Summary of Descriptive Statistics and Statistical Comparisons for Pretreatment and Posttreatment Dependent Measures Across Treatment Conditions*

Dependent measure	Treatment condition	Pre-Tx		Post-Tx	
		M	SD	M	SD
Self-efficacy	WL	48.3 _a	5.1	44.4 _a	5.6
	BT	45.0 _a	6.0	61.1 _b	6.1
	ITGIC	44.1 _a	4.6	59.6 _b	5.7
Coping	WL	278.6 _a	37.2	355.5 _a	52.0
	BT	259.6 _a	29.3	616.4 _b	67.7
	ITGIC	266.7 _a	66.5	564.4 _b	50.5
Likelihood	WL	262.3 _a	65.9	247.3 _a	71.7
	BT	299.6 _a	70.5	138.6 _b	52.6
	ITGIC	231.7 _a	57.9	133.3 _{ab}	40.4
Thoughts	WL	35.7 _a	8.0	30.9 _a	7.1
	BT	50.8 _a	8.0	18.1 _b	4.3
	ITGIC	51.1 _a	8.4	42.0 _{ab}	9.7
Depression	WL	8.1 _a	2.0	7.2 _a	1.5
	BT	14.3 _a	2.2	7.6 _a	1.7
	ITGIC	11.3 _a	3.7	7.7 _a	2.6
Anxiety Sensitivity	WL	41.4 _a	3.6	39.6 _a	3.8
	BT	44.7 _a	2.9	34.7 _a	2.6
	ITGIC	46.1 _a	4.4	44.3 _a	5.2

* Means within time period with different subscripts differ across groups at $p < .05$.

Table 2. Summary of Mean and Standard Deviation Values and Clinical Outcome Comparisons for Weekly Dependent Measures

Dependent Measure	Treatment Condition	Pre-Tx		Post-Tx	
		M	SD	M	SD
Frequency of attacks	WL	2.3 _a	1.5	1.7 _a	.91
	BT	3.2 _a	2.2	0.6 _a	.44
	ITGIC	2.6 _a	2.6	1.0 _a	.51
Average severity of attack	WL	7.5 _a	5.9	3.4 _a	4.3
	BT	7.9 _a	6.1	1.2 _a	2.4
	ITGIC	9.0 _a	5.3	2.2 _a	3.4
Panic attack symptoms	WL	25.6 _a	20.1	8.6 _a	13.4
	BT	47.9 _a	25.6	4.2 _b	11.1
	ITGIC	42.8 _a	29.2	7.1 _{ab}	10.9
Panic attack cognitions	WL	34.8 _a	18.9	17.3 _a	20.5
	BT	49.1 _a	9.1	7.9 _b	13.6
	ITGIC	55.7 _a	15.7	11.4 _b	22.9
Avoidance	WL	47.2 _a	21.3	45.5 _a	18.3
	BT	51.3 _a	18.3	39.2 _a	14.4
	ITGIC	45.4 _a	11.1	38.0 _a	8.7
Panic free at post-tx	WL		1 of 11		4 of 11
	BT		1 of 11		8 of 11
	ITGIC		0 of 9		5 of 9

* Means within time period with different subscripts differ across groups at $p < .05$.

RCT extraction table

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13708, Carlbring et al Treatment of Panic Disorder via the Internet: a randomized trial of a self-help program In <i>Behavior Therapy</i> , 32, 751-764, 2001	Wait-list control	Psychological, self-help treatment Length of the study: between 7 and 12 weeks	Subjects recruited via public advertising and participation included on-line work on a computerized package in the subjects home.	Numbers randomised: 41 Randomisation method: drawing of lots Confirmed ITT analysis. Dropouts' data was utilised as Last Observation Carried Forward	Included if: Diagnosis of PD according to DSM-IV, duration of at least 1 year, age between 18 and 60 years, not suffer from any other psychiatric disorder in immediate need of treatment, have a depression point total on the self-rate version of the Montgomery Asberg Depression Rating Scale of less than 21 points and less than 4 points on the suicide question, Panic Disorder as the primary problem, at least one bull-blown panic attack or one limited symptom attack during the pre-treatment baseline Permitted polypharmacy & therapy: Dosage constant for 3 months before the start of the treatment, patient shad to agree to keep the dosage constant throughout the study, if in therapy, must have been ongoing for more than 6 months (and not CBT type), have had previous contact with physician or other health professional as a result of panic attacks Excluded if: epileptic, kidney problems, strokes, organic brain syndrome, emphysema, heart disorders or chronic high blood pressure	Mean age: 34 years SD=7.5; range 21 to 51 Male/Female: 12 men/29 women Ethnicity: Swedish population	2 weeks	Panic Diary Body Sensations Questionnaire (BSQ); Agoraphobic Cognitions Questionnaire (ACQ); Mobility Inventory for Agoraphobia (MI); Beck Anxiety Inventory (BAI); Beck Depression Inventory (BDI); Quality of Life Inventory (QOLI); treatment credibility scale

Results: treatment, comparator data, dropouts (numbers/percentage and reasons), treatment emergent adverse events (whether spontaneous report or questioned by researcher/treating clinician), investigator's conclusions and reviewers conclusions if different from investigators

Dropouts: 10 subjects did not complete the baseline measures because of lack of access to a computer (n=2), preassessment measurements were felt to be too extensive (n=1), recent commencement of medication (n=3), recently commenced or intensified another unrelated psychotherapy (n=2) and 2 did not give reasons. Another 5 chose not to continue who did give baseline measurements but did not give reasons for discontinuing. Of the randomised patients, 5 dropped out; 3 from the treatment group due to lack of time and one because of a new diagnosis of cancer. The dropout from wait-list did not give a reason.

Patient selection: Computerized interview (Composite International Diagnostic Interview-shortened form: CIDI-sf).

Self-help material: A self-help manual was access via the Web and contained text from a book entitled 'An end to panic: breakthrough techniques for overcoming panic disorder' with 20% of input from Barlow & Craske, 1994's 'Mastery of Your Anxiety and Panic II' and Franklin's 'Overcoming panic: a complete nine-week home-based treatment program for panic disorder' (1996). 6 modules were constructed such that participants could only access the next module by having completed the previous module and completing and returning questions on that module before obtaining the password for the next module. Participants had 14 days to complete each module.

Panic Diary: Significant time x treatment interaction for all full-blown panic attack measures. Limited symptoms attacks (frequency and duration) did not reach statistical significance.

Self-Report Scales: Significant interactions (time x treatment) for all scales excluding the MI where only a trend was identified. (p<.05)

Clinically significant improvement: No occurrence of full-blown panic attacks, and no limited symptoms attacks during the 2 weeks posttreatment.

There were significant improvements on BSQ 81 vs 20%; chi square = 15.23, p<.001

ACQ: 81 vs 45%; chi square = 5.71, p<.05

BAI: 86 vs 30%; chi square = 13.10, p<.001

BDI: 90 vs 40%; chi square = 8.31, p<.01

MADRS-SR: 67 vs 15%; chi square = 11.27, p<.001

Daily Anxiety: 57 vs 10%; chi square = 10.12, p<.01

Frequency of panic attacks: 33 vs 5%; chi square = 5.24, p<.05

No significant improvement on the Mobility Inventory when accompanied (52 vs 30%; chi square = 2.11, p>.10)

And the QOLI (48 vs 30%; chi square = 1.34, p>.10)

Investigators' conclusion: This results of this study 'generally provide evidence for the continued use and development of Internet-based self-help programmes for PD'.

Table 1. Mean (SD) for the Panic Diary for the Treatment and Waiting-List Groups

Measure	Assessment	Group		Interaction $F_{(1,39)}$
		Treatment	Waiting-list	
Daily anxiety	Pre	30.85 (15.8)	28.56 (15.3)	14.85***
	Post	15.91 (13.7)	28.18 (14.1)	
Full-blown panic attacks per week Frequency	Pre	2.19 (4.05)	2.25 (2.8)	4.58*
	Post	0.43 (1.08)	2.325 (3.34)	
Duration (min)	Pre	35.7 (56.6)	44.2 (61.5)	4.22**
	Post	3.63 (8.9)	43.28 (73.5)	
Intensity	Pre	46.5 (31.74)	34.68 (24.3)	9.89**
	Post	12.69 (24.2)	32.94 (28.6)	
Limited symptom attacks per week Frequency	Pre	2.7 (2.1)	4.1 (5.8)	0.003
	Post	2.0 (3.2)	3.4 (6.7)	
Duration (min)	Pre	49.5 (92.3)	46.6 (60.2)	1.6
	Post	14.5 (25.0)	39.9 (49.5)	
Intensity	Pre	29.12 (17.0)	30.44 (19.3)	5.49*
	Post	19.6 (17.1)	34.45 (23.7)	

Note. ^a $F =_{(1,38)}$ One participant from the treatment group was removed from this particular analysis (duration of panic attacks) as the preassessment standardized score was greater than 5 and postassessment data were unavailable.

* $p < .05$; ** $p < .01$; *** $p < .001$.

Table 2. Mean (SD) for BSQ, ACQ, MI, BAI, BDI, QOLI and MADRS-SR for the Treatment and Waiting-List Groups

Measure	Assessment	Group		Interaction $F_{(1,39)}$
		Treatment	Waiting List	
BSQ	Pre	45.3 (7.5)	46.4 (8.7)	34.99***
	Post	29.0 (10.3)	45.1 (12.0)	
ACQ	Pre	31.7 (6.5)	32.9 (9.4)	16.38***
	Post	22.43 (6.0)	30.9 (9.6)	
MI (alone)	Pre	64.4 (23.2)	64.0 (21.9)	12.03**
	Post	47.0 (17.4)	61.4 (20.7)	
MI (accomp.)	Pre	44.4 (13.1)	46.8 (12.7)	3.08#
	Post	37.0 (10.9)	44.3 (14.6)	
BAI	Pre	19.3 (6.2)	21.5 (10.0)	10.97**
	Post	9.8 (8.4)	21.2 (10.4)	
BDI	Pre	11.4 (3.7)	13.1 (6.2)	12.75***
	Post	5.0 (3.6)	12.1 (7.7)	
QOLI	Pre	1.7 (1.1)	1.4 (1.1)	9.52**
	Post	2.2 (1.2)	1.3 (1.2)	
MADRS-SR	Pre	13.1 (4.4)	12.8 (3.7)	17.02***
	Post	7.1 (4.7)	14.1 (6.4)	

Note BSQ = Body Sensations Questionnaire; ACQ = Agoraphobic Cognitions Questionnaire; MI = Mobility Inventory for Agoraphobia; BAI = Beck Anxiety Inventory; BDI = Beck Depression Inventory; QOLI = Quality of Life Inventory; MADRS-SR = self-rated version of the Montgomery Asberg Depression Rating Scale.
* $p < .05$; ** $p < .01$; *** $p < .001$; # $p < .10$.

RCT extraction table

Author (s)	Study (placebo controlled, active comparator etc.)	Type of intervention (pharmacotherapy & name of therapy) Length of study	Setting and location (primary/secondary care or other & country)	Numbers randomised Randomisation method Numbers incl in results analysis (Confirm ITT analysis or % included in results)	Inclusion criteria/ Exclusion criteria Exclusion of depression Permitted polypharmacy Washout period Substance misuse Concordance (compliance)	Mean age (years) Male/female (M/F) ratio Ethnicity	Follow-up period	Main outcome measures (extract data on primary outcome measure only and just note secondary outcome)
Hazen et al, 1996 Anxiety Sensitivity and Treatment Outcome in Panic Disorder	3 treatment groups and wait-list control group	(1) individual self-administration of self-help manual (Coping with Panic) (2) use of manual in self-help treatment group (3) use of manual in treatment group led by professional therapists (4) wait-list control 14 weeks	Referrals to an Anxiety Disorders Clinic (secondary care) and individuals who contacted the Anxiety Disorders Association of Manitoba; Canada	Total randomised = 117 initially randomised of which 106 completed the Anxiety Sensitivity Index (ASI) at pre-and post treatment Randomisation method not reported 106 of 117 included in analysis	Included if: primary diagnosis of panic disorder with or without agoraphobia (DSM-III-R criteria); minimum Grade 8 reading and writing ability; ≥ 18 years; physician agreement Excluded if: presence of organic disease possibly related to panic disorder or might interfere with participation in the study; presence of other psychiatric disorders such as psychotic disorders, substance abuse and current major depressive disorder; presence of significant suicidal risk; involvement with other psychological treatment; current pharmacological treatment for panic disorder apart from low dose benzodiazepines Depression: major depressive disorders were excluded, otherwise no mention of depression as a co-morbidity Permitted polypharmacy: (≤ 20 mg diazepam) or stable doses of antidepressants Washout period: not described Concordance: not reported	Mean age (SD), M/F ratio: 37.12 (9.57), 28/78 Ethnicity: not reported	14 weeks, no follow-up period after treatment end	Anxiety Sensitivity Index (ASI); Fear Questionnaire-Agoraphobia Subscale (FQ-Ag); Sheehan Patient Related Anxiety Scale (SPRAS); Clinical Global Improvement Scale (CGI)
Funding/Support: This work was supported in part by a grant from the Manitoba Health Research Council								
Results: treatment, comparator data, dropouts (numbers/percentage and reasons), treatment emergent adverse events (whether spontaneous report or questioned by researcher/treating clinician), investigator's conclusions and reviewers conclusions if different from investigators								

Means and standard deviations for ASI, FQ-AG and SPRAS							
Measure	Post			Treatment Condition	Pre		
	N	Mean (SD)		N	Mean (SD)		
ASI*	26	17.8 †(11.1)		Professionally led group	26	30.2 (10.9)	
				Self-help group	26	33.5 (10.5)	
	26	23.5† (13.2)		Self-help manual	27	33.7 (12.0)	
	27	26.7 † (13.9)		Wait list	27	36.1 (10.9)	
FQ-Ag				Professionally led group	26	14.4 (9.6)	
	26	5.7 (7.1)		Self-help group	26	14.3 (9.6)	
	26	8.9 (7.3)		Self-help manual	27	16.0 (11.5)	
	27	14.6 (13.1)		Wait list	27	16.3 (10.8)	
SPRAS				Professionally led group	23	51.2 (22.8)	
	26	29.0 (17.7)		Self-help group	24	51.8 (21.9)	
	25	36.9 (24.1)		Self-help manual	26	57.1 (23.5)	
	27	42.4 (23.9)		Wait list	24	55.2 (28.2)	
	27	55.6 (34.2)					
*ASI normative mean (for non-clinical populations) = 19.01 (9.11)							
† means that are not significantly different in multiple comparisons using the Ryan-Einot-Gabriel-Welsh multiple F test following significant repeated measures ANOVA							
Effect Sizes							
Measure	Treatment Condition			Effect Size			
ASI	Professionally led group			1.49			
	Self-help group			1.00			
	Self-help manual			0.72			
FQ-Ag	Professionally led group			1.13			
	Self-help group			0.81			
	Self-help manual			0.25			
SPRAS	Professionally led group			0.78			
	Self-help group			0.55			
	Self-help manual			0.39			
Conclusions: Subjects in the three active treatment conditions had significantly lower anxiety sensitivity scores than the wait-list group at post-treatment. Those who received the professionally led treatment had significantly lower anxiety sensitivity compared to subjects who used the self-help manual independently. There were no significant differences between professional led and self-help group treatment groups and between self-help group treatment group and self-help manual groups. Subjects who showed improvement based on CGI ratings also showed reduction in anxiety sensitivity. ASI was associated with greater effect sizes than the FQ-Ag and SPRAS for all three active treatment conditions.							

Exercise

RCT extraction table

Author (s)	Study (placebo controlled, active comparator etc.)	Type of intervention (pharmacotherapy & name of therapy) Length of study	Setting and location (primary/secondary care or other & country)	Numbers randomised Randomisation method Numbers incl in results analysis (Confirm ITT analysis or % included in results)	Inclusion criteria/ Exclusion criteria Exclusion of depression Permitted polypharmacy Washout period Substance misuse Concordance (compliance)	Mean age (years) Male/female (M/F) ratio Ethnicity	Follow-up period	Main outcome measures (extract data on primary outcome measure only and just note secondary outcome)
11063 Broocks et al Comparison of aerobic exercise, clomipramine, and placebo in the treatment of panic disorder In The American Journal of Psychiatry Volume 155(5) May 1998, 603-609	Active comparator & placebo controlled study	Pharmacotherapy and exercise therapy Exercise (running): 4 mile route – week 1 walking 3-4 times per week, week 2 walking with short 2-4 min bursts of running and by week 4, gradual prolongation of running periods Clomipramine: One capsule of 37.5mg/day increased by one capsule per day the second weeks and the 3 rd week and so forth. Length of study: 10 weeks	Secondary care: patients recruited from an outpatient clinic in a German University hospital	Numbers randomised: 46 Numbers included in results analysis: 46 Confirmed ITT analysis	Included if: Diagnosed with PD or PDA according to DSM-II-R criteria and ICD-10 criteria. Excluded if: Pregnant, lactating, substantial medical illness, bipolar affective disorder, severe major depression, psychotic symptoms, drug dependent, anorexic, or bulimic, body weight below 80% of ideal body weight, taking regular aerobic exercise comparable to the exercise treatment protocol. Washout period: 3 weeks Substance misuses: as stated Permitted polypharmacy: Promethazine (25-50mg) during washout in the case of severe panic attacks.	Mean age: Exercise group: 31.85 (9.5) Clomipramine group: 33.9 (9.2) Placebo group: 34.8 (6.8) Male/female ratio: Exercise group: 6/10 Clomipramine group: 11/4 Placebo group: 6/9 Ethnicity: Not stated	None	Hamilton Anxiety Scale The observer-rated and patient-rated version of the Panic and Agoraphobia Scale The 'rater' version of the CGI

Results: treatment, comparator data, dropouts (numbers/percentage and reasons), treatment emergent adverse events (whether spontaneous report or questioned by researcher/treating clinician), investigator's conclusions and reviewers conclusions if different from investigators

Dropouts: 1 exercise patients in week 1 and 2 between weeks 6 and 8. 4 placebo patients between weeks 6 and 8. Both these dropouts from placebo and exercise dropped out because symptoms had not improved. 2 exercise patients dropped out between weeks 6 and 8 due to 'intermittent disease' that was not treatment related.

Overall dropouts rates for exercise = 31%, placebo = 27% and clomipramine = 0%.

Treatments: Both treatments were significantly superior to placebo and clomipramine was better than exercise at 4 weeks as measure on the rater version of the CGI and on this and the observer-rated and patients-rated versions of the Panic and Agoraphobia Score at 6 and 8 weeks. At the end of the treatment period (week 10), clomipramine measured better than exercise on the rater version of the CGI only.

Side Effects:

Exercise group: transient muscle or joint complaints noted and did not lead to dropout. This effect was noted to disappear on continuance of the exercise regime.

Clomipramine and placebo patients had significantly more side effects including: dry mouth, sweating, mild tremor, dizziness, tachycardia, nausea, constipation, diarrhoea and rarely, impaired erection or ejaculation. It was noted that these effects were highest during the first 4 weeks of treatment after which there was a gradual decline.

Conclusions: . The results indicate that exercise alone is associated with significant treatment gain in patients with panic disorder and may be a particularly useful treatment in those patients who either do not wish or cannot take medication.

Table 2. Baseline Scores and Change Scores at Week 10 on Primary Outcome Measures

Measure	Exercise Group (N=16)		Clomipramine Group (N=15)	
	Mean	SD	Mean	SD
Hamilton Anxiety Rating Scale Score				
Baseline	24.4	8.0	22.5	6.4
Change				
Completer analysis ^b	-13.1	9.5	-14.0	7.3
Last-observation-carried-forward analysis	-12.9	8.4	-14.0	7.3
Clinical Global Impression score (observer rating)				
Baseline	4.4	0.9	4.7	0.6
Change				
Completer analysis ^b	-2.0	0.9	-3.1	0.7
Last-observation-carried-forward analysis	-1.7	1.0	-3.1	0.7
Panic and Agoraphobia Scale score (observer rating)				
Baseline	28.5	9.1	24.4	6.4
Change				
Completer analysis ^b	-13.7	7.5	-16.8	8.5
Last-observation-carried-forward analysis	-12.5	7.7	-16.8	8.5
Panic and Agoraphobia Scale score (patient rating)				
Baseline	27.0	10.2	23.1	5.1
Change				
Completer analysis ^b	-9.8	6.8	-13.4	7.4
Last-observation-carried-forward analysis	-8.8	6.9	-13.4	7.4

aGreenhouse-Geisser adjustments were used in the overall ANOVA. Main treatment effects were compared by repeated measures ANOVA using all six time points (baseline and 2, 4, 6, 8, and 10 weeks); p values of these posts hoc tests were corrected by the Bonferroni-Holm method.

Table 4. Table 2 of Patients With Panic Disorder With or Without Agoraphobia Treated With Exercise, Clomipramine, or Placebo

Placebo Group (N=15)		Repeated Measures ANOVA ^a											
		Group-by-Time Interaction			Exercise Versus Placebo			Clomipramine Versus Placebo			Clomipramine Versus Exercise		
M	SD	F	df	p	F	df	p	F	df	p	F	df	p
20.9	8.5												
0.8	6.9	6.14	10,165	0.0001	6.47	1,33	0.02	11.82	1,33	0.003	0.51	1,33	n.a.
1.9	7.0	8.08	10,205	0.0001	13.36	1,41	0.0007	18.35	1,41	0.0002	0.33	1,41	n.a.
4.2	0.8												
-0.4	1.1	7.16	10,165	0.0001	7.96	1,33	0.0008	62.43	1,33	0.0002	26.92	1,33	0.0002
-0.3	1.0	9.55	10,205	0.0001	9.70	1,41	0.003	83.82	1,41	0.0002	39.04	1,41	0.0002
23.2	7.4												
-2.1	9.0	3.70	10,165	0.0005	4.93	1,33	0.03	23.27	1,33	0.0002	5.63	1,33	0.02
0.5	9.4	5.78	10,205	0.0001	11.22	1,41	0.002	38.36	1,41	0.0002	6.99	1,41	0.01
24.8	6.7												
-1.1	5.7	4.47	10,165	0.0001	2.02	1,33	n.a.	15.50	1,33	0.0008	5.90	1,33	0.02
0.5	7.7	6.20	10,205	0.0001	5.15	1,41	0.03	25.80	1,41	0.0002	7.58	1,41	0.009

^aFor the exercise and placebo groups in the completer analysis, N=11; for the clomipramine group, N=15