Global measures of outcome in a controlled comparison of pharmacological and psychological treatment of panic disorder and agoraphobia in primary care

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SUMMARY

Background. *Panic disorder, with and without agoraphobia, is a prevalent condition which presents primarily in general practice. Previous clinical outcome studies have been conducted mainly in specialist university departments or hospital settings, and have tended to employ complex rating scales that are not well suited for use as outcome measures in primary care.*

Aim. *To evaluate the outcome, in a primary care setting, of fluvoxamine versus cognitive behaviour therapy, each used alone and in combination in a double-blind placebo-controlled framework, balanced for therapist contact.*

Method. *A total of 149 patients satisfying DSMIII-R criteria for panic disorder were randomly allocated to receive one of the following: fluvoxamine, placebo, fluvoxamine plus cognitive behaviour therapy, placebo plus cognitive be-haviour therapy, and cognitive behaviour therapy alone. These five treatment groups represent the minimum number acceptable for such a comparison to be made. All patients received an identical schedule of contact over 13 weeks. Measures of symptom severity, general health and social disruption were taken at entry point and end point; measures of change in symptoms were taken at end point only. Outcome was reported in terms of brief global ratings of severity of illness and change in symptoms, and of ratings of general health and social disruption that are suitable for use in general practice.*

Results. *All active treatment groups showed statistically significant advantages over placebo over a range of outcome ratings. The groups employing cognitive behaviour therapy showed the most robust and consistent response.*

Conclusion. *The brief global measures reported here proved adequate to the task of assessing treatment outcome. Results indicate that treatments including cognitive behaviour therapy can be effective in the treatment of panic disorder and agoraphobia in primary care.*

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Introduction

PANIC disorder with or without agoraphobia is a prevalent disorder, with sufferers making heavy demands on primary care services.[1] Effective treatment is therefore of considerable importance. Research studies have indicated the efficacy of pharmacological treatments,[2] particularly the selective serotonin re-uptake inhibitors.[3] Psychological treatments have been advocated as an alternative to medication,[4] and recent studies have reported immediate and long-term efficacy for cognitive behaviour therapy.[5] Studies investigating the relative and combined efficacies of pharmacological and psychological treatments for panic disorder have been conducted primarily in specialist university clinics or hospital settings, even though the bulk of morbidity in panic disorder and agoraphobia is encountered in general practice.[6] The applicability of this work to the majority of patients seen and treated solely in primary care settings is questionable.[7]

Treatment outcome in clinical trials has generally been reported in terms of percentages of patients free of major panic attacks at the end of treatment, although the reliability of this measure has been questioned.[8] Outcome has also been reported in terms of patient-rated questionnaires, such as the 'fear questionnaire',[9] which concentrates principally on avoidance behaviours and thus represents only a partial assessment of the clinical presentation of panic disorder and agoraphobia. This problem has been rectified in some studies by the use of therapist-rated anxiety scales, often the Hamilton Anxiety Scale.[10-13] The use of such scales is time-consuming and therefore they cannot easily be employed in primary care settings. While pre- to post-treatment reductions on such scales may achieve statistical significance, they do not (in the absence of comparative normative data) give a clear indication of the clinical significance of any improvement, nor do they indicate whether any improvement noted is accompanied by significant improvements in the patient's general well-being and social functioning.

There is a need for more brief global assessment measures in clinical trials of pharmacological and psychological treatments for panic disorder; such measures should be applicable in primary care, and should provide information useful to the management of patients. Some studies have employed global measures of outcome but have used different measures for therapist and patient, thus making comparison impossible.[14,15] Others have employed global measures for therapist only.[16] So far, only one study has employed the same global outcome measure for therapist and patient, although no comparison of ratings was made.[10] Only two studies have employed measures of the impact of treatment on the patient's level of social functioning.[10,16] This is a considerable omission given that one of the main aims of treatment for panic disorder and agoraphobia is to increase patients' level of social functioning and facilitate a return to a more normal lifestyle.

The present study reports on the outcome of a comparison of

pharmacological and psychological treatments for panic disorder and agoraphobia. The study was conducted in the primary care setting, and outcome was reported in terms of global measures of outcome and measures of general well-being and social functioning that are applicable to general practice. Outcome in terms of more traditional rating scales is reported elsewhere.[17]

Methods

Subjects

Patients were referred by general practitioners (GPs) and were considered suitable for pharmacological or psychological treatment. All appointments were in the patients' local general practice clinic. Following initial assessment and referral by their GP, all patients saw a clinical psychologist for a semi-structured interview to ascertain patient characteristics, presenting condition, and severity of illness. Patients were entered into the study if they met the following entry criteria: panic disorder, with or without agoraphobia, conforming to the criteria listed in the *Diagnostic and statistical manual of mental disorders* (third edition, revised (DSMIII-R));[18] a minimum score of 15 on the Hamilton anxiety scale; a maximum score of 20 on the Montgomery Asberg depression rating scale;[19] symptoms lasting three months or longer; no psychotropic medication in the 28 days prior to entry and throughout the study treatment period; aged between 18 and 70 years inclusive.

Over three years, 238 patients were referred by GPs. Of these, 45 did not meet entry criteria; the remaining 193 patients entered the study. Three patients dropped out during the placebo wash-in week and 41 patients dropped out or were lost to end-point assessment. Sixteen patients who were withdrawn early, owing to effectiveness or ineffectiveness of the treatment, but who completed at least 42 days of treatment and who provided adequate end-point data, were included in the sample as 'defined completers'. This methodology avoids an unnecessarily stringent intent-to-treat analysis, as well as the positive bias inherent in full-completers analysis. Analysis was conducted on a sample of 149 completers and defined completers. Patients were randomly allocated to one of five treatment groups: fluvoxamine (FL) (n = 29), placebo (PL) (n = 28), fluvoxamine plus cognitive behaviour therapy (FL+CBT) (n = 29), placebo plus cognitive behaviour therapy (PL+CBT) (n = 33), and cognitive behaviour therapy (CBT) (n = 30). Demographic details of the sample are given in Table 1.

Treatments

All patients were seen to an identical schedule of contact. After one week of single-blind placebo, patients in the FL and PL treatment groups received 12 weeks of either fluvoxamine or placebo. Fluvoxamine was given in 50 mg tablets at an initial dose of 50 mg/day; this was increased by 50 mg to 100 mg/day after 7 days, and by a further 50 mg to 150 mg/day 7 days after this. Thereafter, the dose was maintained at 150 mg/day for the remaining 10 weeks of the study. Medication was discontinued without taper at end point. Medication was supplied in 50 mg tablets. All patients receiving medication (FL or PL) were given the same number of tablets.

Patients receiving CBT alone were seen for an identical schedule of contact but did not receive placebo medication during the wash-in week. The CBT employed emphasized both gross exposure techniques and cognitive and behavioural panic management techniques. The approach in treatment was similar to that of Barlow and co-workers,[20,21] emphasizing the altering of action tendencies associated with panic, and also the hypervigilant and avoidant information-processing strategies and behaviours typical of patients with panic disorder and agoraphobia. Patients were provided with a written treatment manual, which provided information on anxiety and panic attacks and emphasized the importance of patients confronting their panic attacks and attempting to replace avoidant responses, both behavioural and cognitive, with more approach-centred actions.

Patients receiving either FL+CBT or PL+CBT followed the same medication and CBT protocol as that detailed above. The medication was described as adjunctive to the CBT in these groups in an attempt to engage an equal commitment to CBT in the two groups.

Procedure

Following assessment and referral by their GP, patients were seen by the psychologist therapist for initial assessment (day –7), when they were randomized to treatment groups. After a one-week placebo wash-in, or an equivalent time period for the group receiving CBT alone, all patients had further baseline assessments by the psychologist therapist. All medication was dispensed in identical bottles, and compliance was checked by counting returned pills. Over the 12-week treatment period all patients received treatment to an identical schedule of contact, with appointments at days –7, 0, 7, 14, 28, 42, 56 and 70, and end-point assessment at day 84; patients were also seen for follow-up at 6 months. Results for follow-up are reported elsewhere.[17] Individual appointments lasted a minimum of 30 and a maximum of 60 minutes. Patients in the FL or PL alone groups received sessions of equal duration to the three groups receiving CBT; thus all groups received approximately equivalent amounts of therapist contact. Session content for the groups receiving medication alone focused on assessment of current status and progress. Patients in these groups were aware that the psychologist would not offer any therapeutic advice, and no direct advice or reassurance on anxiety management was given.

Measures

Severity of illness was measured using the clinical global impression scale.[22] This seven-point scale gives a range of clinical severity from 1 ('normal') to 7 ('extreme'). Ratings were assigned by the psychologist therapist at day –7 and day 84.

Change in symptoms was measured using the clinical global improvement scale.[22] This seven-point scale rates symptom

Table 1. Demographic features of completers sample (n=149).

	FL n = 29	PL n = 28	FL+CBT n = 29	PL+CBT n = 33	CBT n =30
Mean age (years)	36.62	42.28	37.27	38.81	33.23
Sex	M: 5 F: 23	M: 6 F: 22	M: 7 F: 21	M: 6 F: 27	M: 8 F: 22
Mean duration of panic disorder (years since first panic attack)	7.32	7.74	7.00	6.93	5.11
Mean duration of agoraphobic avoidance (years)	5.04	3.75	6.18	8.35	4.04

FL = fluvoxamine; PL = placebo; CBT = cognitive behaviour therapy.

change on a range of 1 ('very much improved') to 7 ('very much worse'); ratings were assigned by the psychologist therapist and by patients at day 84.

The *General health questionnaire* (GHQ),[23] containing 60 items, was used to provide an overall self-rated measure of psychiatric well-being; it was completed by patients at day 0 and day 84.

The *Sheehan disability scale* (SD)[24] is a simple measure of social functioning. It assesses disruption to daily lifestyle and comprises three 10-point sub-scales on which patients self-rate disruption to work, social life, and family or home life; patients do this on day 0 and day 84.

Statistical analysis

Chi-square tests were used to assess whether significant differences existed between groups in the proportions of patients allocated to the various categories of symptom severity and change in symptoms, before and after treatment. Two-factor analysis of variance within a between-subjects factor treatment group and a within-subjects factor assessment point were conducted. Further analysis was conducted using defined contrasts to investigate differences between drug and placebo groups, both with CBT (FL, FL+CBT versus PL, PL+CBT) (1 -1 1 -1 0) and without CBT (FL vs PL) (1 -1 0 0 0), and between groups employing and groups not employing CBT (FL, PL versus FL+CBT, PL+CBT, CBT) (3 3 -2 -2 -2). Comparisons of ratings within groups, before and after treatment, were carried out using paired two-tailed *t*-tests.

Results

Severity of symptoms

Table 2 presents the ratings of severity of patients' symptoms by the psychologist therapist. Analysis of variance revealed significant group ($F(4,144) = 5.16$, $P<0.001$), time ($F(1,144) = 389.91$, $P<0.0001$) and interaction ($F(1,4) = 10.98$, $P<0.0001$) effects, indicating differential changes between groups. No significant differences existed between groups before treatment (day -7), when the largest proportion of patients for each group fell in the 'moderate' or 'marked' categories. Differences had emerged by day 84, by which time 73–80% of patients in the CBT groups (FL+CBT, PL+CBT, CBT) were rated in the 'normal/borderline' categories, compared with 55% for FL and 29% for PL. Defined contrasts confirmed this finding, there being a significant interaction between group and symptom severity score after treatment ($F(1,144) = 9.98$, $P<0.0001$). The contrast comparing the groups including CBT with those that did not was significant ($P<0.0001$), as was that comparing FL with PL, both without CBT ($P<0.0001$) and with CBT ($P<0.001$). The contrast comparing all four drug groups with CBT alone, i.e. (1 1 1 1 -4), was also significant ($P<0.01$). All five treatment groups showed a significant reduction in symptom severity scores over the course of treatment ($P<0.01$ and below).

Change in symptoms

The change in patients' symptoms rated by psychologist therapist and by patients themselves are given in Table 3. Results for these measures were similar to those for symptom severity. There were significant differences between groups for changes in symptoms rated by both psychologist therapist ($F(4,144) = 9.98$, $P<0.001$) and patients ($F(4,144) = 8.80$, $P<0.001$). Defined contrasts comparing the drug-alone groups (FL, PL) with those including CBT were significant for the ratings of both psychologist therapist ($P<0.0001$) and patients ($P<0.001$). The psychologist therapist rated 85–89% of patients in the CBT groups as 'much improved' or 'very much improved' compared with 75% for FL and 35% for PL. Similarly, patients self-rated 88–90% of the CBT groups as 'much improved' or 'very much improved' compared with 78% for FL and 48% for PL. The contrasts comparing drug with placebo were also significant for the ratings of both psychologist

Table 2. Ratings by psychologist of symptom severity (CG1) before and after treatment.

	Number (%) of patients				
	FL (n = 29)	PL (n = 28)	FL+CBT (n = 29)	PL+CBT (n = 33)	CBT (n = 30)
Day -7					
1-Normal	–	–	–	–	–
2-Borderline	–	–	–	–	–
3-Mild	5 (17)	4 (14)	3 (10)	3 (9)	6 (20)
4-Moderate	9 (31)	18 (64)	15 (52)	16 (49)	16 (53)
5-Marked	15 (52)	4 (14)	11 (38)	11 (33)	5 (17)
6-Severe	–	2 (7)	–	3 (9)	3 (10)
7-Extreme	–	–	–	–	–
			($\chi^2 = 19.570$, d.f. = 12 n.s.)		
Day 84					
1-Normal	11 (38)	3 (11)	17 (59)	15 (45)	18 (60)
2-Borderline	5 (17)	5 (18)	6 (21)	10 (30)	4 (13)
3-Mild	8 (28)	5 (18)	4 (14)	4 (12)	7 (23)
4-Moderate	4 (14)	9 (32)	1 (3)	1 (3)	1 (3)
5-Marked	1 (3)	3 (11)	1 (3)	2 (6)	–
6-Severe	–	3 (11)	–	1 (3)	–
7-Extreme	–	–	–	–	–
			($\chi^2 = 45.947$, d.f. = 20 P<0.001)		

FL = fluvoxamine; PL = placebo; CBT = cognitive behaviour therapy.

Table 3. Ratings by psychologist and patient self-ratings of change in symptom severity after treatment (day 84).

	Number (%) of patients				
	FL (n = 28)	PL (n = 28)	FL+CBT (n = 29)	PL+CBT (n = 33)	CBT (n = 30)
Psychologist ratings:					
1-Very much improved	11 (39)	4 (14)	21 (72)	15 (46)	16 (53)
2-Much improved	10 (36)	6 (21)	5 (17)	13 (39)	10 (33)
3-Minimally improved	3 (11)	10 (36)	3 (10)	3 (9)	4 (13)
4-No change	3 (11)	6 (21)	–	1 (3)	–
5-Minimally worse	1 (4)	–	–	–	–
6-Much worse	–	2 (7)	–	1 (3)	–
7-Very much worse	–	–	–	–	–
	(χ^2 = 48.281, d.f. = 20, P<0.001)				
Patient self-ratings:					
1-Very much improved	14 (52)	6 (22)	24 (83)	23 (72)	17 (57)
2-Much improved	7 (26)	7 (26)	2 (7)	5 (16)	10 (33)
3-Minimally improved	4 (15)	7 (26)	1 (3)	2 (6)	3 (10)
4-No change	2 (7)	4 (15)	2 (7)	2 (6)	–
5-Minimally worse	–	2 (7)	–	–	–
6-Much worse	–	1 (4)	–	–	–
7-Very much worse	–	–	–	–	–
	(χ^2 = 41.268, d.f. = 20, P<0.01)				

FL = fluvoxamine; PL = placebo; CBT = cognitive behaviour therapy.

therapist and patients when drug-alone groups were compared without CBT (psychologist (P<0.001), patient (P<0.001)) and with CBT (psychologist (P<0.0001), patient (P<0.01)).

For psychologist therapist ratings, the contrast comparing all four drug groups with CBT alone was also significant (P<0.05). The psychologist therapist and patients' ratings of change in symptoms following treatment showed considerable agreement (Pearson r = 0.89, P<0.01).

General health questionnaire

Table 4 gives the means and standard deviations for total GHQ score before and after treatment. Analysis of variance revealed significant group (F(4,144) = 2.64, P<0.05), time (F(1,144) = 68.51, P<0.0001) and interaction (F(1,4) = 2.58, P<0.05) effects, indicating differential changes between groups. No differences existed between groups before treatment. Significant differences between groups emerged after treatment (day 84), (F(4,144) = 6.38, P<0.0001). Defined contrasts again yielded an identical pattern to previous measures, with a superiority for CBT groups over drug-alone groups (P<0.0001), and a superiority of FL over PL, both with CBT (P<0.01) and without CBT (P<0.01). The contrast comparing CBT alone with all four drug groups was also significant (P<0.05). Comparison of scores before treatment (day 0) with after treatment (day 84) showed a significant reduction in GHQ scores for all groups, with the exception of placebo.

Sheehan disability scale (SD)

The means and standard deviations for scores on this scale before and after treatment are given in Table 4. Analysis of variance for the work scale revealed a significant time (F(1,144) = 79.18, P<0.001) and interaction (group x time) (F(1,4) = 4.20, P<0.01) effect. The social-life scale also revealed significant time (F(1,144) = 146.41, P<0.001) and interaction (F(1,4) = 7.13, P<0.001) effects. The home/family-life scale showed significant group (F(4,144) = 2.95, P<0.05), time (F(1,144) = 144.79, P<0.0001), and interaction (F(1,4) = 4.26, P<0.01) effects.

All groups except PL showed a significant reduction in scores on work (all P<0.001) and social life (all P<0.0001). All groups including PL showed a significant reduction in home/family life scores (P<0.01 and below).

Differences existed between groups at day 84 on work (F(4,144) = 4.36, P<0.01), social life (F(4,144) = 6.12, P<0.0001) and home/family-life (F(4,144) = 6.11, P<0.0001).

Defined contrasts showed a pattern identical to that of previous measures. The CBT groups were superior to the drug-alone groups for work (P<0.01), social life (P<0.0001), and home/family life (P<0.0001). Contrasts also revealed a superiority of FL over PL without CBT for work (P<0.01), for social life (P<0.01), and for home/family-life (P<0.01). Results were similar for the comparison of FL and PL with CBT: for work, P<0.01; for social life, P<0.001; and for home/family life, P<0.01.

Discussion

This study is the first to compare a pharmacological and a psychological treatment for panic disorder and agoraphobia in the primary care setting. Outcome is expressed in terms of brief global measures that are suitable for use in general practice. Results of the study indicate that these measures, despite their relative simplicity, are able to indicate differential outcomes between groups. Similar measures (particularly psychologist and patient ratings) have previously been shown to be sensitive to change in generalized anxiety disorder patients who are treated in primary care by either pharmacological or psychological interventions.[25]

All measures employed in the current study gave virtually the same result, with no disagreement between measures on the main pattern of findings. This again attests to the robustness of these

Table 4. Means and standard deviations (sd) for GHQ and Sheehan disability scale before and after treatment.

	FL (n = 29)	PL (n = 28)	FL+CBT (n = 29)	PL+CBT (n = 33)	CBT (n = 30)
GHQ:					
Day 0	19.56 (17.35)	22.82 (17.29)	19.93 (16.79)	19.78 (15.95)	21.47 (16.39)
Day 84	8.17 (14.50)	19.39 (20.25)	4.55 (11.88)	5.94 (10.95)	3.97 (6.43)
P<	0.01	n.s.	0.0001	0.0001	0.0001
Sheehan disability scale:					
Work:					
Day 0	4.66 (3.23)	4.64 (3.13)`	5.24 (3.35)	5.46 (3.23)	4.80 (3.42)
Day 84	2.24 (2.85)	4.29 (3.41)	1.38 (2.77)	210 (2.58)	1.87 (2.64)
P<	0.001	n.s.	0.0001	0.0001	0.0001
Social life:					
Day	05.03 (2.76)	5.18 (3.72)	6.97 (2.92)	6.12 (3.43)	5.73 (2.86)
Day 84	2.24 (2.76)	4.57 (3.23)	1.31 (2.25)	2.24 (2.92)	1.70 (2.37)
P<	0.0001	n.s.	0.0001	0.0001	0.0001
Home life:					
Day 0	4.03 (2.84)	5.57 (3.20)	5.17 (2.78)	5.39 (3.21)	4.60 (2.90)
Day 84	1.93 (2.87)	4.04 (3.34)	1.00 (2.09)	1.46 (2.12)	1.60 (2.22)
P<	0.0001	0.01	0.0001	0.0001	0.0001

FL = fluvoxamine; PL = placebo; CBT = cognitive behaviour therapy; GHQ = general health questionnaire; n.s. = not significant.

relatively simple measures.

Results indicate that all four active treatment groups (FL, FL+CBT, PL+CBT and CBT) are superior to the placebo (PL) group, but that those treatment groups that include CBT (FL+CBT, PL+CBT, CBT) show a consistent and significant trend of superiority over those taking fluvoxamine alone (FL). This reinforces previous findings suggesting an efficacy for CBT in the treatment of panic disorder and agoraphobia. Some aspects of this finding warrant further discussion. First, an attempt has been made in this study to balance therapist contact across all treatment groups; thus patients receiving FL or PL alone had appointments of the same duration as those in the CBT groups. Hence, the superiority for the CBT groups found here cannot be attributed solely to the increased therapist contact that CBT entails. However, the balance for therapist contact employed in this study has meant that the drug-alone groups received appointments that were significantly longer than those employed in standard general practice. As such, the FL and PL groups in this study may not be truly representative of these treatments as employed in primary care. To rectify this we intend to study a further two groups of patients given FL or PL alone to the same schedule of contact as was used in this study, with the exception of duration of appointment, which will be reduced to 5–10 minutes. This will constitute a more realistic test of the performance of the drug-alone treatments in primary care.

A second aspect of the current study, worthy of comment, also relates to therapist contact. All of the treatment groups in this study were seen on nine occasions (including initial assessment, but excluding follow-up) — substantially fewer than the 12–16 sessions employed in previous studies of CBT in the treatment of panic disorder and agoraphobia.[11,12,14,15] The CBT employed in the current study might reasonably be referred to as brief CBT. Our finding of strong efficacy for CBT is therefore of considerable relevance for primary care. We are currently conducting further investigations of reduced-contact CBT in the treatment of panic disorder and agoraphobia in primary care. Such investigations will continue to employ brief global measures of the type shown to be of value in the current study.

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