Panic Management, Trazodone and a Combination of Both in the Treatment of Panic Disorder

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Background—The aim of the study was to assess the short-term efficacy of panic management, trazodone and a combination of both in the treatment of panic disorder. In none of the treatments exposure in vivo instructions were given. Method—Patients were diagnosed using DSM-III-R criteria for panic disorder. A randomly assigned, comparative design was used in which patients were their own controls. Fifty-two of 60 outpatients who entered the study, completed the 6-week baseline and 6-week active treatment period. Outcome measures included self-report measures for panic frequency, panic intensity, agoraphobic anxiety and avoidance, and depression. Results—There was significant improvement on all symptom dimensions during treatment in contrast to the baseline period. No evidence for a differential efficacy of the three treatments was found. Both dropout and improvement rates were substantially lower than those reported in previous studies of behaviour therapy and antidepressants or a combination of both in panic patients. Conclusion—It is concluded that the short-term effects of panic management and trazodone without concurrent exposure in vivo instructions are marginal and comparable to those of placebo as reported in previous studies. It is suggested to evaluate the efficacy of a prescriptive simple component therapy versus a multicomponent psychotherapy for panic.

INTRODUCTION

The efficacy of antidepressants and (cognitive-) behavioural treatments of panic disorder has been demonstrated in various controlled studies (Michelson and Marchione, 1991; Klerman, 1992). Trazodone is a triazolopyridine derivate of which the antidepressant effect is comparable to that of imipramine and other tricyclic antidepressants (Georgotas et al., 1982). Trazodone has been demonstrated to be a safe drug with a wide therapeautic index and several controlled studies have shown marked anti-anxiety effects (Liebowitz and El-Mallakh, 1989). Although trazodone is still regularly prescribed in anxiety disorder, the efficacy of trazodone in treating panic disorder has only been assessed in two studies. Charney et al. (1986) investigated the comparative efficacy of imipramine, alprazolam and trazodone in a non-randomized trial of 8 weeks after a baseline period of placebo administration of 3 weeks in 74 patients with panic disorder. Each patient also attended weekly behaviour therapy sessions. Relative to imipramine and alprazolam, trazodone was not effective and poorly tolerated. Mavissakalian et al. (1987) treated 20 patients with panic disorder in a single-blind uncontrolled trial of trazodone during 8 weeks, after a baseline period of placebo.

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administration of 2 weeks. No concurrent behavioural instructions were given. The 11 patients who completed the trial showed significant improvement on all symptom dimensions.

Psychological panic management usually consists of several components such as hyperventilation provocation training, breathing retraining, relaxation training as well as cognitive restructuring. Although panic management is widely used, a conclusion on its relative efficacy with respect to psychopharmacological therapy cannot be drawn on the basis of available studies, because the efficacy of panic management without additional exposure in vivo instructions in comparison to psychopharmacological therapy has never been investigated (Van Balkom et al., 1995).

Given the conflicting results on the efficacy of trazodone alone or combined with behavioural instructions and the lack of studies into the efficacy of psychological panic management alone in comparison to psychopharmacological therapy, it was decided to investigate the short-term efficacy of trazodone, panic management and a combination of both without concurrent exposure instructions in the treatment of panic disorder.

METHODS

Patients were consecutive referrals to the Psychiatric Outpatient Clinic of Leiden University. Inclusion criteria were: (a) a DSM-III-R (American Psychiatric Association, 1987) diagnosis of panic disorder with (PDA) or without agoraphobia (PD) as assessed with the Anxiety Disorder Interview Schedule (ADIS-R) (Di Nardo et al., 1983; De Ruiter, 1987); (b) age between 18 and 60; (c) duration of panic symptoms for at least 3 months; (d) if on low maintenance doses of benzodiazepines for extended periods of time agreement to keep the dosage constant throughout the study; (e) informed consent obtained. Exclusion criteria were: (a) the presence of concomitant psychosis, major depression, alcohol abuse or dependence according to DSM-III-R criteria; (b) suffering from one of the following somatic disorders: hyperthyroidism, pheochromocytoma, bronchial asthma with medication use and angina pectoris; (c) already using trazodone at the start of the study (patients using other antidepressants were instructed to stop these within 2 weeks).

The following variables were assessed: patients kept a daily record of panic attacks. In the analyses, panic attack frequency and mean panic intensity during the first 2 weeks of the baseline period (week 1 and 2) will be compared with the frequency and intensity during the last 2 weeks of the baseline period (week 4 and 5) and the week before and after the last therapy session (week 11 and 12). On a slightly modified version of the original Watson and Marks scale (WMS) (Watson and Marks, 1971), patients rated their level of anxiety and avoidance behaviour in five standard situations (Emmelkamp, 1979). The Dutch version of the ZUNG Depression Scale (ZUNG) (Zung, 1965; Dijkstra, 1974) was used in order to assess the level of depression during the last 2 weeks. After each week of active treatment with trazodone, reported use in mg/day was recorded by the therapist (week 7 to 11) or the research assistant (week 2). Moreover, during each therapy session therapists asked patients to rate the severity during the last week, except during panic attacks, of one of the following somatic symptoms: drowsiness, light-headedness, dry mouth, blurred vision, constipation, nausea or vomiting, headache, heart palpitations, priapism, rash or other somatic symptoms.

The study employed a randomly assigned, comparative design in which patients were their own controls. At the beginning of the study patients were randomly assigned to therapy conditions and therapists. The first assessment (pretreatment I at week 0) was followed by a no-treatment baseline period of 6 weeks. After the second assessment (pretreatment II at week 6) a treatment phase of 6 weeks followed after which the third assessment was scheduled (posttreatment at week 12).

In each of the three treatment conditions, six individual therapy sessions of 45 min were provided once per week in order to control for therapy time and therapist attention. In none of the conditions exposure instructions were given.

Trazodone (TR)

In the first treatment session the rationale of prescribing antidepressants for panic attacks was explained and possible side-effects of trazodone were mentioned. Trazodone was administered on a flexible dosage regimen. Dosages were adjusted by the treating psychiatrist according to therapeutic effect and side-effects. Trazodone was started at 50 mg to be taken at bedtime and could be increased to 100 mg during the first week in the absence of side-effects or marked clinical improvement. If maximal clinical improvement was not obtained, trazodone had to be increased by 50 mg every week to a maximum dosage of 300 mg/day.
Therapists were only allowed to answer questions or to give advice concerning the use of trazodone. In relation to other topics, therapists had to adopt a supporting and empathic stance.

**Panic Management (PM)**

In the first session patients received the treatment manual *Managing Anxiety* (Butler, 1985) and the treatment rationale was explained to the patient. The following therapeutic techniques were used: voluntary hyperventilation and explanation of how hyperventilation symptoms or arousal symptoms plus catastrophic cognitions cause panic attacks (session 1 and 2); breathing retraining (session 1 and 2); progressive relaxation (session 2, 3, 4 and 5); identification of catastrophic cognitions (session 3); coping distraction (session 4); modification of catastrophic cognitions (session 5); transfer and generalization of panic management skills (session 6).

**Combined Therapy (CT)**

In the first session the rationale for prescribing antidepressants for panic disorder, as well as panic management was explained. Trazodone and panic management were administered in the same way as described above.

Two therapists, one male and one female senior psychiatrist both experienced in treating PD, conducted the individual sessions. Detailed treatment manuals were provided to therapists to ensure treatment integrity.

Treatment results were analysed with a three (group) by three (time) split-plot design using multivariate and univariate analyses of variance. An endpoint analysis was performed, which substitutes the last available pretreatment II assessment for the (unavailable) posttreatment assessment for dropouts during treatment. *A posteriori* contrasts were calculated by use of *t*-tests. For non-Gaussian variables, non-parametric analyses were used based on ranks to check the results of parametric analyses. In case of comparable results these analyses are not reported.

**RESULTS**

The sample consisted of 50 patients (26 men, 34 women) with an average age of 35.6 years ± 7.8 (range 21–58). Mean duration of their panic attacks was 6.2 years ± 6.8 (range 0.25–23). The group comprised 51 PDA and nine PD patients. Fifty patients were married or living together, six were single and four were divorced. Twenty-five patients were taking low potency benzodiazepines at the start of the study.

No significant differences between the three treatment groups with regard to demographic and clinical variables, as well as pretreatment measurements on the dependent variables were found.

Eight patients, four in the TR group and four in the CT group, dropped out of the study. One patient in the TR group no longer suffered from panic attacks after the baseline period. This patient was not included further in the data analysis of treatment results. Of the remaining seven dropouts, three patients completed only 1 week of trazodone treatment, three patients 2 weeks, and one patient 4 weeks of treatment. These seven patients terminated trazodone treatment prematurely because of marked side-effects (increased anxiety (*N* = 2), nausea (*N* = 1), blurred vision (*N* = 1), rash (*N* = 1), headache and heart palpitations (*N* = 1) and lightheadedness and drowsiness (*N* = 1)).

A Fisher exact probability test revealed that significantly more patients treated with trazodone (*N* = 3) or combined treatment (*N* = 4) prematurely terminated therapy in comparison to patients receiving panic management alone (*N* = 0) (*p* < 0.05).

Results of the treatment are presented in Table 1. An endpoint analysis revealed a significant overall time effect (*F*(10,216) = 4.62, *p* < 0.001). Subsequent univariate analyses of variance showed a highly significant time effect on all self-report measures. *A posteriori* contrasts indicated no significant change on these measures during baseline. However, all contrasts comparing the posttreatment mean on these measures with the pretreatment II mean were significant (0.001 < *p* < 0.02).

The differential effects of the treatment regimes are reflected in the time by group interaction. None of the interaction effects proved to be significant. Also, none of the group effects reached significance.

Next, the effect size Cohen’s *d* (Cohen, 1988) was calculated within each of the treatment conditions by subtracting posttest from pretreatment II test and then dividing the difference through the pooled standard deviation (see Table 1). The effect sizes are small to medium.

At week 12 the mean dosage was 178 mg/day. The side-effects (as stancardly assessed by the therapist at each therapy session) during week 6 can be regarded as a baseline measure because during
Table 1. Means and standard deviations on self-report measures at pretreatment I, pretreatment II and post-treatment for the three treatment groups

<table>
<thead>
<tr>
<th>Measure</th>
<th>Pre I Mean</th>
<th>Pre I SD</th>
<th>Pre II Mean</th>
<th>Pre II SD</th>
<th>Post Mean</th>
<th>Post SD</th>
<th>ANOVA Time effects F (df 2,112)</th>
<th>ANOVA Time effects p</th>
<th>Effect size (Cohen’s d)</th>
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<tr>
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<td>12.3</td>
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<td></td>
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<td>12.2</td>
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<td>49.6</td>
<td>9.0</td>
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<td>44.1</td>
<td>9.8</td>
<td></td>
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<td>0.46</td>
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</tbody>
</table>

TR, trazodone (N = 19); PM = panic management (N = 20); CT, combined treatment (N = 20); TG, total group (N = 59).

that week patients did not use trazodone. A dry mouth was the only somatic symptom which was significantly enhanced during treatment with trazodone in comparison to the baseline (t(31) = 2.15, p < 0.05), while headache (t(31) = 2.12, p < 0.05) and heart palpitations (t(31) = 2.49, p < 0.05) were significantly reduced.

In 12 patients dosages could not be increased by a further 50 mg because of side-effects although maximal clinical improvement was not obtained. The mean dosage of these patients was 148 mg/day in comparison to 197 mg/day in the other 20 patients who completed trazodone treatment (t(30) = 1.78, p = 0.09). An analysis of covariance revealed no significant differences in posttreatment panic frequency between both groups (F(1,31) = 0.75, p = 0.39).

DISCUSSION

Significantly more patients prematurely terminated treatment with trazodone (16%) or trazodone in combination with behaviour therapy (20%), while none of the patients treated only with behaviour therapy dropped out. However, the absolute dropout rate of 18% in the present study is substantially lower than reported by Charney et al. (1986) (44% at a mean dosage of 238 mg/day) and Mavissakalian et al. (1987) (36% at a mean dosage of 281 mg/day) after 6 weeks of treatment with trazodone. Although in the present study also a starting dose of 50 mg/day was used, it is conceivable that more side-effects and dropouts would have been observed if in the course of treatment a fixed dosage regimen resulting in a higher maximum dosage had been used.

With respect to the efficacy at the end of treatment, it was found that during treatment—irrespective of treatment regime—patients reduced their panic and concomitant psychopathology in contrast to the no-treatment baseline period. In the absence of an independent placebo or no-treatment control condition and by the lack of differential treatment effects, it cannot be excluded that the observed improvement is caused by nonspecific
treatment effects of spontaneous remission. However, the present study employed an intensive time-series design and the finding that during the 6-week baseline period no significant changes in panic and concomitant psychopathology were observed makes it unlikely that the significant improvement on all symptom dimensions during the second 6-week treatment period is mainly due to time effects.

On the other hand, it can be argued that therapeutic improvement was primarily due to non-specific treatment factors. Treatment in the total group was associated with small to medium effect sizes (Cohen, 1988) for respectively panic frequency (0.19–0.54), agoraphobic avoidance (0.17–0.24) and depression (0.36–0.56), while meta-analyses on the efficacy of treatment of PD with antidepressants and anxiety management with exposure in vivo (Mattick et al., 1990; Cox et al., 1992; Clum et al., 1993; Van Balkom et al., 1995) report large effect sizes of at least 0.80 for panic, agoraphobia and depression. In fact the effect sizes found in the present study are more comparable to those reported in the meta-analysis of Mattick et al. (1990) which also gives effect sizes calculated within treatment conditions for placebo treatment (panic: $d = 0.29$ (present study: 0.40); agoraphobia: $d = 0.42$ (present study: 0.18–0.74); depression: $d = 0.40$ (present study: 0.36)). Probably, the relatively low effect sizes for the agoraphobia measures are due to the fact that PD patients in the present sample showed only mild levels of agoraphobia in comparison to previous studies using the same measures (e.g. Emmelkamp et al., 1992) leaving little room for improvement in agoraphobia.

The active treatment phase of 6 weeks is, compared with other trials with antidepressants for panic disorder, relatively short (Michelson and Marchione, 1991; Klerman, 1992). It is conceivable that in a more extended trial a higher medication dosage could have been achieved and that more patients would have had the opportunity to be on the maximum dosage of 300 mg/day for more than 1 week allowing more time for maximal clinical improvement to become manifest. However, it should be recognized that although high dosage levels of trazodone may produce a better response, they may also be associated with higher dropout rates due to side-effects.

Also with respect to panic management, it can be questioned whether treatment was delivered in sufficient amount to have an optimal effect. The panic management condition consisted of several components: hyperventilation provocation training followed by breathing retraining and relaxation training, as well as cognitive restructuring. In comparison to previous studies of combined treatments for panic, the treatment duration of six sessions in 6 weeks is relatively short (Michelson and Marchione, 1991).

About 50% of our panic patients found the symptoms induced by voluntary hyperventilation to be similar to those occurring spontaneously during panic attacks. Since voluntary hyperventilation was the only interoceptive exposure procedure used in our study, the conditioned association between somatic cues and panic attacks could only be weakened by repeated interoceptive exposure in a subsample of our patients. Moreover, the addition of breathing retraining and relaxation training to repeated voluntary hyperventilation has the potential to increase overall treatment effectiveness provided that an adequate level of training is provided and the anxiety management techniques are consistently applied to the interoceptive cues which elicit the panic response (Acierno et al., 1993). In retrospect, it can be questioned whether patients were trained in a sufficient degree to apply these panic management techniques systematically to anxiety-inducing interoceptive cues.

Finally, it can be argued that theoretical refinements and extensions of the cognitive model of panic since the start of the present study question the theoretical basis of the panic management regime. Recently, panic attacks are explained as the consequence of a positive feedback loop between the perception of internal cues, their association with threat, and the patient's anxiety response to these symptoms which in turn leads to further bodily sensations (Clark, 1986). The most important techniques in this approach are identifying and challenging misinterpretations of bodily sensations by a combined use of the Socratic dialogue and behavioural experiments. Recent studies suggest that these 'pure' cognitive treatments are highly effective in reducing panic with 75–95% of patients becoming panic free after 3 months of treatment (Michelson and Marchione, 1991; Magraf et al., 1993). For example, in a recent comparison of cognitive therapy, applied relaxation and imipramine in the treatment of panic disorder 75–90% of the patients treated with cognitive therapy were panic-free at 3 to 15 months follow-up (Clark et al., 1994).

In the present study cognitive procedures operated primarily at the level of substituting negative thoughts or self-statement (e.g. replacing catastrophic cognitions with positive self-instructions.
or using coping distraction), while catastrophic inferences were not actively challenged and, consequently, may have remained intact. These interventions are primarily derived from a behavioural model, where anxious thinking is considered to be a maladaptive behavioural habit (Biran, 1988). Because they are targeting the most superficial cognitive level they may be less efficacious (Michelson and Marchione, 1991) and may even inadvertently contribute to the avoidance of symptoms, and not to the corrective experiences of symptoms (Hoffart, 1993).

It is concluded that without concurrent exposure in vivo instructions both trazodone and panic management are only marginally effective in treating panic disorder. Multicomponent psychological treatments which include exposure-based techniques, breathing retraining and relaxation techniques, as well as cognitive interventions theoretically compromise the most important procedures available to treat panic. In developing shorter forms of treatment, assessing the effectiveness of prescriptively matching panic treatments with subtypes of patients seems a promising approach. For example, in the absence of catastrophic cognitions during panic attacks, but clear recognition of symptoms after voluntary hyperventilation, interoceptive exposure with breathing retraining and relaxation training is likely to be indicated and effective. On the other hand, when an individual reports catastrophic cognitions, cognitive therapy aimed at altering catastrophic misattributions seems warranted. There is a dearth of controlled studies evaluating the efficacy of a single component therapy directed toward those areas most prominent for each patient versus a multicomponent therapy addressing all possible components for panic.

REFERENCES


