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Double-blind comparison of 30 and 60 mg tranylcypromine daily in patients with panic disorder comorbid with social anxiety disorder

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ABSTRACT

Our objective was to explore the dose–response relationship in patients with panic disorder and social anxiety disorder comorbidity (DSM-IV). After 1 week of no-drug washout, 36 such patients were assigned to a double-blind controlled comparison of the effects of 30 mg and 60 mg of tranylcypromine, and were followed up for 12 weeks. The main instrument used to measure the number of panic attacks was the Sheehan Panic and Anticipatory Anxiety Scale. The primary outcome measure for social anxiety disorder symptoms was the mean change from baseline in the Liebowitz Social Anxiety Scale (LSAS). After 12 weeks of treatment, panic attacks were reduced 69.6% from baseline in the 30-mg group ($n=19$) compared with a 74.8% reduction in the 60-mg group ($n=17$). Twelve patients (70.6%) of the higher dose group and 14 patients (68.4%) of the lower dose were completely free of panic attacks. There was no difference in efficacy between the tranylcypromine groups in the panic disorder symptoms. The 60-mg dose was more efficacious as measured by the LSAS scores, showing a significant difference in relation to the lower group. Mean change from baseline in LSAS total score (mean ± SD) for 30-mg group was -17.9 ± 14.7 and for the 60-mg group was -35.0 ± 14.8. The social anxiety symptom scale showed a two-fold greater change with the 60-mg dose, and the 30-mg dose group could be considered the equivalent of a placebo control group. Tranylcypromine – 60 mg daily – was found effective in the treatment of panic disorder and social anxiety disorder comorbidity.

1. Introduction

The concept of comorbidity has clinical and theoretical implications (Frances et al., 1990). Situational panic attacks are common in social anxiety disorder (Liebowitz et al., 1985), and non-situational panic attacks occur frequently in anxiety disorders as well as in panic disorder (Liebowitz et al., 1985; Frances et al., 1990). The diagnostic dilemma presented by patients who exhibit both panic disorder and agoraphobia and who avoid certain performance or social situations has been addressed by Liebowitz et al. (1985). The term "primary social anxiety disorder" was suggested for those patients who fear scrutiny or evaluation by others and whose anxiety is confined to social situations or anticipation. "Secondary social anxiety disorder" would apply to those patients who have panic attacks in nonsocial situations and fear/avoid situations where an exit is not available. Occasionally, cases of anxiety disorder comorbidity are described as a clinical curiosity (Goldstein, 1987). Goldstein (1987) presented three cases in which the DSM-III classificatory distinctions are blurred, and the course of the illness seems to involve temporary overlapping manifestations of panic attacks, social anxiety disorder and agoraphobia. The association between lifetime anxiety disorders and personality disorders among adults in the community was explored by Goodwin and Hamilton (2003). Their data were drawn from the National Comorbidity Survey ($n=5877$), a representative community sample of adults aged 15–54 in the 48 US states. Out of the 3.3% of adults with antisocial personality disorder (ASPD), over half (54.33%) had a comorbid anxiety disorder (lifetime). Similarly, 42.31% of adults with a history of conduct disorder (CD) (9.4%) who did not meet criteria for ASPD had a lifetime anxiety disorder. Social anxiety disorder and post-traumatic stress disorder were associated with significantly increased odds of ASPD. The comorbidity of anxiety disorders and ASPD was associated with significantly higher odds of major depression, substance use disorders, and suicide ideation and attempt compared with odds among those without both disorders. These data provide initial evidence of an association between post-traumatic stress disorder and social anxiety disorder, and an increased likelihood of ASPD among adults in the community, after adjustment for comorbid affective and substance use disorders. Adults with ASPD and comorbid anxiety had significantly higher levels of comorbid

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major depression, alcohol dependence, and substance dependence and substantially higher rates of lifetime suicidal ideation and suicide attempts compared with adults with ASPD or anxiety disorders alone or with neither disorder.

Over the last two decades the combination of selective serotonin reuptake inhibitors (SSRIs) with cognitive-behavioural therapy (CBT) has been considered an efficacious option for the treatment of anxiety disorders (Roy-Byrne et al., 2006). The clear efficacy and increased tolerability of the SSRIs over previous treatments (tricyclics and monoamine oxidase inhibitors — MAOI) have led to the widespread conclusion of their being the first-line choice in all these disorders (Roy-Byrne et al., 2006). In a clinical setting the treatment of choice depends on a number of issues, including adverse effects, efficacy, and the presence of concomitant syndromes. It is crucial to provide a risk-benefit assessment for each patient, and the treatment choice should be based on individualized assessment. From this point of view, there is still a place for older drugs such as the MAOIs in certain cases, and they should be studied in special populations.

Arnot (1960) was the first to describe the anxiolytic effect of a MAOI. Sheehan et al. (1980) showed that phenelzine was superior to imipramine in relation to several panic disorder measures, including reduction of disability, and this finding renewed interest in this class of drug for treating panic disorder. Since then, MAOIs have been shown to be efficacious in social anxiety disorder (Deltito and Perugi, 1986; Liebowitz et al., 1986; Versiani et al., 1988; Liebowitz et al., 1988; Versiani et al., 1992) and panic disorder or comparable disorders (Sargant, 1969; Tyrer et al., 1973; Sheehan et al., 1980; Versiani et al., 1987; Tyrer and Shawcross, 1988).

The first double-blind study with patients with social anxiety disorder (Liebowitz et al., 1988) compared phenezine and atenolol with placebo in the treatment of 74 patients with social anxiety disorder. The average dose was 76 mg/day for phenelzine. At the end of the 16-week treatment period, about 2/3 of the patients treated with phenelzine showed a significant improvement, whereas less than 1/3 improved with atenolol and placebo.

Although MAOIs are an effective antipanic agent (Sargant, 1969; Sheehan et al., 1980; Versiani et al., 1987; Tyrer and Shawcross, 1988), they are generally used as second line agents due to their associated adverse reactions and dietary restrictions (Jann and Kurtz, 1987; Bechelli et al., 1989). A disadvantage of the conventional irreversible MAOIs is the risk of hypertensive crises when combined with dietary tyramine (Tyrer and Shawcross, 1988; Bechelli et al., 1989). There are no important therapeutic differences between the MAOIs, and there is growing evidence that MAOIs are somewhat more effective than tricyclic antidepressants in the treatment of anxiety disorders and when phobic anxiety is an important component of a depressive disorder (Jann and Kurtz, 1987; Tyrer and Shawcross, 1988).

Patients that present the characteristic features of both social anxiety disorder and panic disorder (Liebowitz et al., 1985) might benefit most from a treatment suited for both disorders. This study was designed to explore the dose–response relationship for tranylcypromine in patients with panic disorder (with and without agoraphobia) with social anxiety disorder comorbidity — DSM-IV. Our hypothesis is that a higher dose of tranylcypromine may be necessary to the treatment of social anxiety disorder symptoms than for panic disorder symptoms considering not only the phobic avoidance but the panic attack and the anticipatory anxiety. This different response to a lower and a higher dose may be associated with the dopaminergic system in social anxiety disorder (Ressler and Nemeroff, 2000).

2. Methods

The patients were randomly selected at the Laboratory of Panic & Respiration of the Institute of Psychiatry of the Federal University of Rio de Janeiro. Our clinic receives many anxiety disorder patients, and we had a reasonable number of newly admitted panic disorder and social anxiety disorder comorbid patients to choose for this trial. Participants were men and women, aged between 18 and 60, who met DSM-IV criteria for panic disorder, with or without agoraphobia, and social anxiety disorder generalized subtype, both determined by the Structured Clinical Interview (First et al., 1997) for DSM-IV. Patients needed to have a minimum of four panic attacks, at least one of which was unanticipated, during the 4 weeks before the initiation of the non-drug washout period, and at least three panic attacks during the 1-week non-drug washout before the open treatment. At the end of the washout, patients needed to score at least 18 on the Hamilton Anxiety Rating Scale (HAMA; Hamilton, 1959) and below 17 on the 21-item Hamilton Depression Rating Scale (HAMD) (Hamilton, 1960). Patients had to have a negative result for a urinary screen for benzodiazepines and barbiturates on baseline.

Women of childbearing potential had to be using an effective method of birth control. Pregnant or nursing women were excluded from participation. Patients who met DSM-IV criteria for current major depression, bipolar disorder, obsessive-compulsive disorder, schizophrenia, delusional or psychotic disorders, organic brain syndrome, severe personality disorder, epilepsy, or substance abuse or dependence (during the previous year) were also excluded. Patients with comorbid dysthymia, generalized anxiety disorder or past major depression could be included if the panic disorder and social anxiety disorder were judged to be the principal diagnosis. Other reasons for exclusion included unstable medical conditions; hypersensitivity or other medical contraindications to MAOI therapy; participation in an investigational drug study within 6 months of study entry; previous treatment with tranylcypromine; concomitant treatment with any psychotropic drug or psychotherapy during the study; use of any regular antipsychotic, antidepressant, regular benzodiazepine or nonbenzodiazepine anxiolytic medication within 4 weeks, or fluoxetine within 5 weeks of the first administration of study medication; or the presence of suicidal risk.

After complete description of the study to the subjects, written informed consent was obtained. The protocol complying with the principles laid down in the Declaration of Helsinki was approved by our local Ethics Committee.

2.1. Drug administration

In a double-blind design, patients were randomly assigned to 12 weeks of treatment with either tranylcypromine 30 mg/day or tranylcypromine 60 mg/day. They were informed about the probable side effects including the symptoms of hypertensive crisis and precautions that they should follow (diet restrictions, drug interactions, nifedipine for hypertensive crisis, etc.). Study capsules contained either 10 mg of tranylcypromine or placebo to preserve the double-blind condition after the 30 mg daily. Patients were instructed to take the capsules twice daily after breakfast and after lunch. Those randomized to tranylcypromine 30 mg/day received 20 mg/day for the first week; in the absence of dose-limiting adverse experiences, this was increased to 30 mg/day for the second week and this dose was continued for the rest of the study. The patients randomized to tranylcypromine 60 mg/day received 20 mg/day for the first week, 40 mg/day for the second week, and 60 mg/day for the third week, and this dose was continued for the rest of the study. All patients received the same number of capsules per day. The doses were not decreased in the case of limiting adverse experiences (any side effect that disturbed the patient and could not be easily managed); if adverse events occurred, the patients were dropped from the study.

2.2. Efficacy assessments

This is a double-blind trial as the raters were blinded to the dose group and the patients and the medical assistant were also blinded to the dose level to which patients were assigned. The raters were blind during the analysis of the diaries and throughout the statistical analysis. Patients were seen for evaluation at baseline and at the end of weeks 1, 2, 4, 6, 8, and 12.

2.2.1. Primary instruments

All independent raters were trained in the instruments used in this trial in our Laboratory. Before the trial began and twice during it, we had theoretical and practical sessions of training to standardize our recordings.

The main efficacy instrument for panic disorder symptoms was the Sheehan Panic and Anticipatory Anxiety Scale (Sheehan, 1983), from which the principal efficacy measure – the percentage of patients with no panic attacks – was obtained. Throughout the study, participants maintained a daily diary, in which the frequency of panic and limited symptom panic, panic attacks, and duration of anticipatory anxiety were recorded by the patient. These data were subsequently reviewed by the investigators and used to complete the Panic and Anticipatory Anxiety Scale scores. Baseline Panic and Anticipatory Anxiety Scale scores were based on the 1-week non-drug washout period. Anticipatory anxiety was recorded as the percentage of time in each 24 h spent worrying about having a panic attack.

The outcome measures for the social anxiety symptoms were the mean change from baseline in the Liebowitz Social Anxiety Scale (LSAS) total score (Liebowitz et al., 1988), and the patient-rated visual analogue scale scores reflecting self-confidence in social interactions, anticipatory anxiety, acute anxiety reactions in social situations, and dysphoria following anxiety reactions.

2.2.2. Secondary instruments

Clinicians rated global severity by means of the Clinical Global Impression Severity Scale (Guy, 1976) (CGI-S, ranging from 1 — not at all ill to 7 — extremely ill). Global change from the baseline assessment was rated by means of the Clinical Global Impression Improvement Scale (Guy, 1976) (CGI-I, ranging from 1 — very much