



## A DOUBLE-BLIND PLACEBO-CONTROLLED TRIAL OF PAROXETINE IN THE MANAGEMENT OF SOCIAL PHOBIA (SOCIAL ANXIETY DISORDER) IN SOUTH AFRICA

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**Background.** Social phobia, also known as social anxiety disorder, is a highly prevalent disorder with significant morbidity. Patients with social phobia frequently develop co-morbid psychiatric disorders such as depression and substance abuse, and the disorder impacts significantly on social and occupational functioning. It has been suggested that the selective serotonin reuptake inhibitors (SSRIs) are useful in the management of this disorder, but few controlled trials have been undertaken in this regard. There are also few data on the pharmacotherapy of social phobia in South Africa.

**Methods.** A double-blind randomised placebo-controlled multi-site flexible-dose trial of paroxetine was undertaken over 12 weeks among patients with a primary diagnosis of social phobia. Primary response measures were the Global Improvement item on the Clinical Global Impression scale (CGI) and mean change from baseline in the patient-rated Liebowitz Social Anxiety Scale (LSAS) total score. Ninety-three patients participated at 9 South African sites; their data are reported here.

**Results.** There was a significant drug effect on both the CGI Global Improvement score and the LSAS at 12 weeks. In addition, there was no significant difference in overall rate of adverse experiences between those on paroxetine and those on placebo.

**Conclusions.** Paroxetine is both effective and safe in the acute treatment of social phobia. The findings here are consistent with those of previous controlled studies of the SSRIs as well as with previous work done in the USA on the use of paroxetine in the treatment of this disorder. Early diagnosis and treatment of social phobia should be encouraged. However, further research on long-term pharmacotherapy of social phobia is needed.

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Social phobia, also known as social anxiety disorder, has increasingly been recognised as a highly prevalent disorder that is accompanied by significant morbidity. A recent national study found that lifetime prevalence of social phobia ranged from 0.5% to 2.6%,<sup>1</sup> although some studies have found rates of social phobia to be as high as 13.3%.<sup>2</sup> Social phobia is a chronic and serious disorder — patients frequently develop co-morbid psychiatric disorders such as depression and substance abuse,<sup>3</sup> and social anxiety symptoms impact significantly on social and occupational functioning.<sup>4</sup>

Unfortunately, social phobia remains poorly recognised and inadequately treated in the primary care setting.<sup>5</sup> The characteristic fear of social and performance situations where exposure to unfamiliar people or to scrutiny occurs<sup>6</sup> may not be recognised as representing a psychiatric disorder by either the patient or the clinician. Nevertheless, there is growing evidence that specific pharmacotherapeutic and psychotherapeutic interventions can treat social phobia effectively.<sup>7</sup>

The first medications shown to be effective in controlled trials of social phobia were the irreversible monoamine oxidase inhibitors (MAOIs).<sup>8</sup> Dietary and other restrictions necessitated by these medications have led to interest in the more recently introduced reversible MAOIs, although evidence for the efficacy of these agents in the management of social phobia has been conflicting.<sup>9-12</sup> High-potency benzodiazepines also appear to be effective in managing social phobia,<sup>13,14</sup> but the dependency potential of these agents is worrisome.

Preliminary evidence of serotonergic involvement in social phobia<sup>15</sup> provides some theoretical justification for using the selective serotonin reuptake inhibitors (SSRIs).<sup>13</sup> Indeed, a range of uncontrolled trials have suggested that these agents are useful in the treatment of social phobia.<sup>16-24</sup> Nevertheless, there are relatively few controlled trials of the SSRIs in this regard. While fluvoxamine<sup>25</sup> and sertraline<sup>26</sup> were found to be more effective than placebo in the acute treatment of this disorder, sample sizes in these two studies were small ( $N = 30$  in the fluvoxamine study and  $N = 12$  in the sertraline study).

Two double-blind randomised placebo-controlled multi-centre trials of paroxetine in patients with a primary diagnosis of social phobia have recently been completed, one in North

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America and one in Europe and South Africa.<sup>27</sup> In this paper we report on the findings for the South African sites that participated in the latter study. Given the universally high prevalence of this disorder, its underdiagnosis in primary care settings, and the lack of previous research in South Africa, we concluded that publication of these data might help to raise awareness of social phobia and its available treatment options.

## METHODS

### Sites and subjects

Thirty-nine sites, located in Belgium, France, Germany, Ireland, South Africa, Spain and the UK, participated in the trial. There were 9 sites in South Africa; 3 in State medical schools and 6 in private practitioner settings. Investigators were chosen for their interest in the study and their ability to enter eligible patients. All investigators met to ensure consistent study procedures; they also received intensive training in diagnosing social phobia using the Mini International Neuropsychiatric Interview (MINI).<sup>28</sup>

Two hundred and ninety adult outpatients were enrolled in the study, of whom 93 were from South Africa. (Demographic details are supplied in the Results section.) All subjects met *Diagnostic and Statistical Manual (DSM-IV)*<sup>6</sup> criteria for social phobia. Subjects had to be at least 18 years of age, and subjects over 65 had to be able to tolerate a paroxetine starting dose of 20 mg daily and to be without renal or hepatic impairment (test results had to be within twice the upper limit of normal). All subjects gave written informed consent after approval of the protocol by an ethics committee.

Patients were excluded on a number of grounds, including: (i) co-morbid psychiatric conditions — i.e. if they had Axis I disorders such as major depression, dysthymia, simple phobia, obsessive-compulsive disorder, panic disorder as a primary disorder in the past 6 months, or body dysmorphic disorder; if there was a history of schizophrenia or bipolar disorder; if they met *DSM-IV* criteria for substance abuse in the 3 months before the trial or substance dependence in the 6 months preceding the trial; or if they posed a current, serious suicidal or homicidal risk in the investigator's judgment; (ii) co-morbid medical conditions — i.e. if there were any serious medical disorders or conditions that would preclude paroxetine administration; if there was a history of seizure disorder (except for febrile seizures in childhood); if they had clinically significant abnormal laboratory or electrocardiographic findings at baseline; or if they were of child-bearing potential and had a positive pregnancy test or were lactating or were not practising a clinically accepted method of contraception; (iii) treatment requirements and history — i.e. if they required concomitant therapy from psychoactive medications other than chloral hydrate; if they were receiving psychotherapy (except stabilised psychotherapy regimens that were ongoing for at

least 6 months); if they had had previous treatment for social phobia with SSRIs at a dose and for a duration that would have been adequate to show a response (equivalent to 3 months' treatment with fluoxetine 20 - 40 mg); if they had taken psychoactive drugs within 14 days of baseline or depot neuroleptics within 12 weeks of baseline; if they had used an investigational drug within the past month (or 5 half-lives, whichever was the longest); if they had received electroconvulsive therapy within 3 months of entry into the study; or if they were previously unresponsive or intolerant to paroxetine.

### Visits and medication

At the screening visit, which included a full medical and psychiatric history and physical evaluation, patients were assessed for eligibility to participate in the study. Thereafter, patients underwent a 1-week single-blind placebo run-in. Patients who scored 1 (very much improved) or 2 (much improved) on the Global Improvement item of the Clinical Global Impression (CGI)<sup>29</sup> scale at the subsequent (baseline) visit were excluded.

At the baseline visit patients were randomised by computer-generated code to paroxetine or placebo for 12 weeks. Clinic visits then took place at weeks 1, 2, 3, 4, 6, 8 and 12 for assessments of efficacy, safety, concomitant medications and general compliance with study procedures. A telephonic consultation took place at week 10 to assess safety, concomitant medications and general compliance. Visits to each investigator site were undertaken in order to monitor investigator adherence to protocol.

Paroxetine and placebo were provided as identical capsules. Paroxetine was initiated at a dosage of 20 mg daily for 2 weeks, after which the clinician could titrate it upwards by 10 mg each week to a maximum of 50 mg daily, according to clinical response and tolerability. One 10 mg dose reduction was also allowed in response to adverse events. Paroxetine was tapered over 3 weeks at the end of the 12-week study. Patients were instructed to return medication packs with any unused drug to the investigator at each visit, and a record of supplies dispensed, taken, and returned was made at each visit.

A patient could withdraw or be withdrawn from the study prematurely for the following reasons: (i) adverse experience; (ii) ineffectiveness of treatment (patient's perception); (iii) protocol deviation, including non-compliance; and (iv) lost to follow-up.

### Efficacy and safety

The CGI scale was administered by the treating clinician at baseline and at each subsequent clinic visit. The Liebowitz Social Anxiety Scale (LSAS),<sup>30</sup> the Social Avoidance and Distress Scale (SADS),<sup>31</sup> and the Sheehan Disability Scale (SDS)<sup>32</sup> were completed by the patient at baseline and at each subsequent clinic visit.