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Paroxetine in the treatment of dysthymic disorder without co-morbidities: A double-blind, placebo-controlled, flexible-dose study

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ABSTRACT

Few published studies have evaluated selective serotonin reuptake inhibitors in dysthymia without current co-morbid major depression. In this 12-week study, 40 dysthymic patients were randomly assigned to either placebo ($n = 19$) or 20–40 mg/day of paroxetine ($n = 21$). At endpoint, the paroxetine group showed significantly greater improvement on the Clinical Global Impression Scale, Beck Depression Inventory, and Quality of Life Enjoyment and Satisfaction Questionnaire ($p < 0.05$), and a trend to superiority over placebo on the Hamilton Depression Rating Scale. Response and remission were significantly higher with paroxetine than placebo ($p < 0.05$). There were no significant differences in drop out rates or frequency of adverse effects, except for excessive sweating (greater with paroxetine, $p = 0.04$). Reporting of multiple side effects was also higher with paroxetine than with placebo ($p = 0.02$). Paroxetine is more effective than placebo in improving symptoms and quality of life in dysthymia, and is generally tolerable.

1. Introduction

Dysthymia (low-grade chronic depression) tends towards milder symptoms and a chronic course compared to major depressive disorder (MDD), but with similar functional impairment (Freeman, 1994; Haykal and Akiskal, 1999). The utility for pharmacotherapy for dysthymia is often debated, as the impaired mood, interpersonal dysfunction, and anhedonia often seen in dysthymics are frequently perceived as characterological deficits, not as symptoms (Akiskal, 1990). Although psychotherapy can be helpful, previous randomized controlled trials (RCTs) have demonstrated the benefit of pharmacotherapy, and that prolonged remission without medication is unusual (Browne et al., 2002; De Lima et al., 1999). Selective serotonin reuptake inhibitors (SSRIs) are first-line agents due to their high tolerability (Akiskal, 2001), including fluoxetine (Serrano-Blanco et al., 2006), sertraline (Ravindran et al., 2000), and citalopram (Hellerstein et al., 2004).

Paroxetine, a potent SSRI, has shown superiority over placebo in many mood and anxiety disorders, including MDD (Wagstaff et al., 2002), but RCTs of its use in dysthymia are limited. In patients with MDD and dysthymia, paroxetine was inferior to venlafaxine (Ballús et al., 2000), but comparable to moclobemide (Pini et al., 2003). An open trial found paroxetine and amisulpiride equally effective in dysthymia (Rocca et al., 2002a), while an RCT found paroxetine alone as effective as their combination (Rocca et al., 2002b).

There are two previous published placebo-controlled RCTs of paroxetine in dysthymia, but results are mixed. Patients had either dysthymia or minor depression and co-morbid anxiety, but no current MDD or other Axis I or II disorders. In the first study, with elderly patients, paroxetine was superior in efficacy to placebo but remission rates were similar (Williams et al., 2000). The parallel study with younger patients (18–59 years) found that paroxetine and placebo had similar efficacy but remission was higher with paroxetine (Barrett et al., 2001).

The negative results may be partly explained by the presence of co-morbid anxiety, which predicts poorer response and remission in dysthymia (Akiskal and Cassano, 1997; Svanborg et al., 2008), as is also seen in other depressive and anxiety disorders with anxiety co-morbidities, despite the efficacy antidepressants may show in the individual disorders (Baldwin and Lopes, 2009; Boylan et al., 2004; Hofmeijer-Sevink et al., 2012). In an attempt to replicate and extend the Barrett et al. (2001) study, the current study evaluated the efficacy and tolerability of paroxetine in adult dysthymics without current co-morbidities. The primary hypothesis was that paroxetine is more effective than placebo in improving depressive symptoms and is well tolerated.

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2. Methods

This single-site, investigator-initiated, 12-week, double-blind, placebo-controlled, parallel-group, randomized study was conducted at a university hospital and approved by the institutional research ethics board. After written informed consent, patients entered a one-week, single-blind, placebo washout phase before randomization to paroxetine 10 mg/day or placebo (1:1 ratio). Dosage was titrated every two weeks, based on response and tolerability. The minimum and maximum allowed doses were 20 mg/day and 40 mg/day, respectively.

2.1. Subjects

Patients (aged 18–60 years) were recruited who met DSM-IV-TR criteria for dysthymic disorder (American Psychiatric Association, 2000), as confirmed by the Mini International Neuropsychiatric Interview (Sheehan et al., 1998), and who scored ≥13 and ≤22 on the 17-item Hamilton Rating Scale for Depression (HAM-D 17) (Hamilton, 1967).

Exclusion criteria included diagnosis of a major depressive episode within the past six months, other current Axis I or II disorders, current use of antidepressants, history of sensitivity to SSRIs, and previous non-response to an adequate trial of paroxetine.

After washout, subjects scoring ≥13 on the HAM-D 17 were randomized to treatment.

2.2. Efficacy and safety evaluations

Patients were evaluated at screening, baseline and weeks 1, 2, 4, 6, 8 and 12. Clinician-rated measures included the HAM-D 17 and the CGI. Patient-rated measures included the Beck Depression Inventory (BDI) (Beck et al., 1961), and the Quality of Life Enjoyment and Satisfaction Questionnaire (Q-LES-Q) (Endicott et al., 1993). The primary efficacy variable was the change in score from baseline to Week 12 on the HAM-D 17.

Data were analyzed on an intent-to-treat basis using the last observation carried forward (LOCF) technique. Repeated measures analyses of variance (ANOVA) were used to analyze longitudinal efficacy outcomes on primary and secondary efficacy variables. The model included fixed categorical effects of treatment, visit and treatment by visit interactions, and a continuous fixed covariate of baseline. Where the sphericity assumption was violated, a Greenhouse-Geisser correction was applied. Secondary analyses included post hoc pairwise comparisons between paroxetine and placebo treatments on change from baseline to Week 12, and chi-square or Fisher's exact tests to compare response, side effect and drop-out rates.

3. Results

3.1. Patient characteristics

Forty-five patients (aged 19–59 years) were recruited. Five withdrew voluntarily during washout. The rest were randomized to receive placebo ($n = 19$) or paroxetine ($n = 21$) (See Fig. 1). Both groups had comparable demographics and baseline efficacy parameters (see Table 1). Thirty-three (33) patients completed the full 12 weeks of treatment. The remaining seven patients completed at least 8 weeks of treatment, were deemed evaluable, and were included in the intent-to-treat analysis (see Table 2).

3.2. Efficacy

No group differences were found on the HAM-D 17. However, a non-significant trend favoring paroxetine over placebo was noted ($F(2.39,86.04) = 2.79$, $p = 0.08$, $\eta^2 = 0.072$) (see Fig. 2).

Significant group differences favoring paroxetine were found on the CGI-I ($F(1,37) = 4.72$, $p = 0.03$, $\eta^2 = 0.11$), BDI ($F(1.57, 57.28) = 5.45$, $p = 0.02$, $\eta^2 = 0.14$) and Q-LES-Q ($F(1.58, 56.83) = 12.14$, $p = 0.001$, $\eta^2 = 0.25$) with improvement seen as early as Week 8 on the BDI and Q-LES-Q, and by Week 12 on the CGI (see Figs. 3–5). It is also of note that quality of life was rated higher in the placebo group than in the paroxetine group at baseline ($p < 0.05$), but at post-treatment, there was no statistical change in this measure in the placebo group, whereas the paroxetine group improved significantly ($p = 0.001$). In addition, functional components of the Q-LES-Q also showed significant improvement with paroxetine (but not placebo) in domains such as work ($F(1,37) = 4.74$, $p = 0.04$, $\eta^2 = 0.11$), social relationships ($F(1,37) = 9.51$, $p = 0.004$, $\eta^2 = 0.20$), leisure activities ($F(1,37) = 5.46$, $p = 0.03$, $\eta^2 = 0.13$), and daily functioning ($F(1,37) = 9.52$, $p = 0.004$, $\eta^2 = 0.20$). Similarly, other submeasures of the Q-LES-Q, which relate directly to symptom improvement, such as mood ($F(1,37) = 8.21$, $p = 0.007$, $\eta^2 = 0.18$), sense of well-being ($F(1,37) = 8.52$, $p = 0.006$, $\eta^2 = 0.19$) and life satisfaction ($F(1,37) = 9.61$, $p = 0.004$, $\eta^2 = 0.21$), also improved significantly with paroxetine, but not with placebo. Functional improvement, per the Q-LES-Q correlated highly with symptom improvement from baseline on both the HAM-D 17 ($r = -0.64$, $p < 0.01$) and the BDI ($r = -0.76$, $p < 0.01$).

Non-parametric analyses indicated that percentage of patients who either responded to treatment (a ≥50% decrease from baseline scores on the HAM-D 17 and/or or a CGI-I rating of 1 or 2) or achieved remission (a score of ≤8 on the HAM-D 17), were both significantly higher with paroxetine (response = 66.7%; remission = 57.1%) than with placebo (response = 31.6%; remission = 21.1%) ($\chi^2(1, n = 40) = 4.91$, $p = 0.03$; $\chi^2(1, n = 40) = 5.41$, $p = 0.02$ respectively).

3.3. Dose and tolerability

The mean final dose was 33.33 mg/day for paroxetine and 35.25 mg/day for placebo. Information on adverse events was obtained at each study visit through specific physician inquiry about side effects, and reported effects were then rated as related or non-related to study medication. The most common side effects, e.g. headache, nausea, sexual dysfunction, diarrhea, sweating and fatigue, were reported by three or more patients (see Table 3). Less frequent side effects, reported by two or fewer patients, included dry mouth, decreased appetite, weight gain, dizziness, and vomiting.

While the number of patients reporting at least one adverse event did not differ between groups ($\chi^2(1, n = 40) = 2.52$, $p = 0.11$), the number of patients experiencing multiple side effects was significantly higher with paroxetine than with placebo ($\chi^2(1, n = 40) = 5.16$, $p = 0.02$). Of note, six participants reported sexual side effects. All were male, precluding any analysis based on gender, and five out of six were in the paroxetine group. The side effects included diminished sexual arousal ($n = 1$); delayed ejaculation ($n = 3$); decreased libido ($n = 1$); and inability to orgasim ($n = 2$), all of which were deemed "possibly related" or "probably related" to study medication. However, other than excessive sweating, which was greater with paroxetine ($p = 0.04$), there was no statistical difference in the incidence of individual side effects between the groups. The results of these non-parametric analyses of adverse events should be interpreted with some caution due to the small sample size, but it is notable that no patients withdrew from the study due to side effects.