

A prospective randomized single-blind, multicenter trial comparing the efficacy and safety of paroxetine with and without quetiapine therapy in depression associated with anxiety

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OBJECTIVE: To evaluate quetiapine as an adjunct to paroxetine in patients with comorbid depression and anxiety.

METHOD: Prospective, multicenter, single-blind trial of patients with DSM-IV major depression and associated anxiety, who were randomized to an 8-week treatment with paroxetine alone (n = 54) or paroxetine + quetiapine (n = 58). Quetiapine was dosed to 200 mg/day and paroxetine to 60 mg/day, as required.

RESULTS: Decrease in HAM-A scores was significantly greater in the combined therapy group than with paroxetine alone at weeks 2, 4, 6 and LOCF (P < 0.008). Decrease in HAM-D scores was significantly greater in the combined therapy group than with paroxetine alone throughout the study period (P < 0.008). Regarding adverse events, it was found that increases in anxiety and insomnia were more prevalent in the paroxetine only group, while increased appetite was more prevalent when quetiapine was added (P < 0.05).

CONCLUSION: Quetiapine added to paroxetine is well tolerated and may speed up and improve response in patients with comorbid depression and anxiety. (Int J Psych Clin Pract 2004; 8: 1–7)

Keywords
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paroxetine

INTRODUCTION

In current clinical practice, initial antidepressant treatment is effective in 60–70% of patients with depression.¹ The remaining patients are usually prescribed another antidepressant drug or approached with other forms of treatment, such as an atypical antipsychotic, lithium, thyroid hormone or electroconvulsive therapy.² When depression is associated with anxiety, treatment becomes more challenging.^{3,4} A patient with depression associated with anxiety is considered

more resistant to standard antidepressant therapy than one with a primary, sole diagnosis of major depression.⁵

Tricyclic antidepressants, monoamine oxidase inhibitors, and selective serotonin reuptake inhibitors (SSRIs) have been shown to be effective in the treatment of coexisting anxiety and depression.⁶ However, the side effects of the first two limit their use,⁶ and SSRIs may produce a transient increase in anxiety symptoms at the beginning of the treatment.⁷ On the other hand, benzodiazepines are useful for the acute treatment of anxiety, and buspirone for chronic generalized

anxiety, but neither agent has been found to be effective for the long-term treatment of depression.⁶ Furthermore, the addictive potential of benzodiazepines and their side effects restrict their use.⁸

Several studies have highlighted the potential of atypical antipsychotics in alleviating depression and hostility in both psychotic and non-psychotic patients,^{9–11} suggesting their use in treating anxiety associated with depression. Quetiapine, a dibenzothiazepine derivative atypical antipsychotic drug, has been evaluated for the management of patients with psychotic disorders,^{12,13} but there is no published study showing the efficacy of quetiapine in depressed non-psychotic patients with anxiety.

The aim of the present study was to evaluate the benefit of adding quetiapine to standard antidepressant therapy with paroxetine, an SSRI, in patients with depression associated with anxiety. Our hypothesis was that the addition of quetiapine to paroxetine treatment increases the effectiveness of therapy on anxiety and is tolerated well.

MATERIALS AND METHODS

STUDY DESIGN

This was a prospective multicenter, single blind, randomized clinical trial. A total of 120 outpatients (18 to 65 years) were enrolled in the trial at three different study centers. The enrolled patients were diagnosed as major depression by the investigator, according to the Diagnostic and Statistical Manual of Mental Disorders-Fourth Edition (DSM-IV). The patients with major depression were applied Hamilton Depression Scale (HAM-D) and Hamilton Anxiety Scale (HAM-A) by the rater in study center. If HAM-D scores on items 10 and 11 (associated with anxiety) ≥ 2 and HAM-A score ≥ 26 , which indicate depression associated with anxiety, patient would be included to the study with the decision of investigator. Exclusion criteria were; HAM-D score on item 3 (related to suicide) > 2 , any psychotic disorder, treatment with any psychotropic medication in the last month, severe or chronic physical illnesses, abnormal results in routine hematological, biochemical, thyroid function tests or urinalysis, history of manic episodes, history of alcohol/substance abuse in the year preceding study enrollment, pregnancy and lactation.

The patients were randomly allocated to either "paroxetine" or "paroxetine+quetiapine" groups. A randomization list was built in accordance with the principles of basic randomization with a fixed block size of four: namely, with every cycle of four consecutive patients, it was ensured that half would be allocated to one group and the other half to the other group. The master list was built for 120 patients and split into three, each for 40 patients and these lists were distributed to three study centers. When the investigators checked the study selection criteria and confirmed that the patient had met them, they then allocated the patient into the first "empty" place in the list.

All study patients received paroxetine, in the same manner, regardless of the study group they were allocated to. The initial daily dose of paroxetine was 20 mg; a 10-mg increment at 1–2-week intervals or according to clinician judgment, to a maximum daily dose of 60 mg, was allowed. In the paroxetine+quetiapine group, quetiapine was added to paroxetine, with an initial daily dose of 25 mg. Allowed dose increments of quetiapine was 25–50 mg daily, with weekly intervals, to a maximum daily dose of 200 mg.

The study duration was 8 weeks with follow-up visits at weeks 1, 2, 4, 6 and 8. At each study center two staff members were in charge; one of them (investigator) was responsible for the clinical evaluation of the patients and the other (rater) was responsible for application of psychometric scales. At each patient visit, the investigator evaluated the history of the patient with regard to clinical status, compliance, the presence of adverse events, concurrent illnesses and concomitant medications and made her/his decision about the dosage of study medications according to the patient's clinical status. Then a rater applied HAM-A and HAM-D scales to the patients. The "investigators" and "raters" were blinded to each others' evaluation results, meaning that the investigators did not know the scores of the scales and the raters did not know the medications the patient received. In order to assure inter-rater consistency, at the study start-up meeting investigators and raters came together and reviewed the application of HAM-A, HAM-D and Clinical Global Impression (CGI) scales. Then the raters watched video displays of patient interviews and rated these patients. Inconsistently scored items were re-evaluated and the reasons for inconsistency were discussed and corrected.

Treatment groups were compared in terms of their efficacy as shown by the changes in HAM-A scale as primary outcome measure, and secondarily in terms of the changes in HAM-D scale and CGI as secondary outcome measure.

Side effect profiles were expressed as frequency of adverse events (AEs). AEs were recorded using direct questioning based on a symptom/AE list, together with spontaneous reports by the patient. Patients were systematically questioned for the presence of the following events; increase in anxiety, sexual problems, retardation, sedation, insomnia, agitation, dyspeptic problems, nausea, increased bowel gas, diarrhea, constipation, appetite changes, headache, dizziness, vertigo, tremor, excessive sweat, mouth dryness, visual acuity problems, skin rash, orthostatic hypotension, amenorrhea, and cardiovascular problems. AEs reported during treatment visits were not documented as a new 'AE' if they had been reported at baseline visit.

The study was approved by Ethics Committee located at the project coordinator's site. This study was conducted in compliance with ICH GCP Guidelines and the Edinburgh, Scotland 2000 revision of the Declaration of Helsinki. Subjects who met eligibility criteria were given written information sheets, including the details about the background, rationale and design of the study, expected benefits

and possible risks related with study drugs, patients' rights and responsibilities, etc. Then additional questions raised by the patients were answered and, for the patients who accepted to participate in the study, informed consent forms signed by the patient, the investigator and the witness were collected and kept in study files.

STATISTICAL ANALYSIS

Since major study parameters (scale scores and change in scores) showed non-normal distribution, mostly nonparametric analytical methods were applied.

Group proportions were compared by means of chi-square tests.

Dichotomic variables (gender, absence of psychiatric disorder, etc.) in the study groups were compared with the chi-square test. If the expected values were less than 2 in any cell and/or less than 5 in 50% or more cells in 2×2 contingency tables, Fisher's exact test was used. Ordinal variables (education level, income level, etc.) were compared with Mantel-Haenszel chi-square test for linear association.

The majority of the variables showed non-normal distribution, therefore group means were compared by Mann-Whitney *U*-test. Since mean baseline HAM-D scores of the study groups were found to be significantly different, analysis of covariance (ANCOVA) was used to test the difference of mean HAM-D scores. For major study parameters, the last observations were carried forward to week 8 and an analysis of data from these last observations carried forward (LOCF) was also performed. The number of statistical tests performed for individual study parameters was seven, since there were six measurements corresponding to study visits and an additional LOCF value. Therefore, in order to avoid significance inflation due to multiple comparisons, the type I error level was adjusted downward to 0.008 as calculated by the formula $(1 - (0.95)^{\text{the number of comparisons}} = 7)$. For study parameters (HAM-A, HAM-D and

CGI, statistical significance was assigned to *P* values less than 0.008, for other variables, statistical significance was assigned to *P* values less than 0.05.

The sample size was determined based on the assumption that a clinically significant difference in HAM-A score change between the two groups would be 5 with a standard deviation of 7. The sample size calculation assumptions were based on the values from the literature^{14,15} and also the average number of major depression patients complying with study criteria in study centers per year. Type I error was accepted as 0.05 and the power of the study was set to 0.90. Based on these assumptions, a minimum of 42 subjects/group would fulfill the requirements. In order to compensate for the estimated drop-out rate of 30%, 60 patients were planned to be recruited for each group.

RESULTS

Of 120 enrolled patients, eight were not included in the analysis groups (five patients due to withdrawal of consent within the first week and three due to randomization error). Therefore a total of 112 patients constituted the study population (54 patients in the paroxetine group and 58 patients in the paroxetine + quetiapine group).

Mean ages of the patients were 35.9 ± 13.7 and 33.9 ± 10.6 in the paroxetine and paroxetine + quetiapine groups, respectively (Student's *t*-test, $t = 0.854$, $P = 0.40$). The study groups were also comparable with regard to gender distribution and other patient characteristics (Table 1). In the paroxetine + quetiapine group, two patients dropped out because of AEs and nine patients did not attend the eighth week visit; whereas in the paroxetine only group, a total of 17 patients dropped out from the study, nine because of the AEs, one due to withdrawal of consent and seven who did not attend the final visit.

Table 1
Patient characteristics in study groups

	Paroxetine		Paroxetine + quetiapine		χ^2	P value
Gender					2.955	0.086
Female	44	(81.5%)	39	(67.2%)		
Male	10	(18.5%)	19	(32.8%)		
Education level					1.613	0.45
Uneducated	5	(9.3%)	4	(6.9%)		
Primary education	32	(59.3%)	41	(70.7%)		
University	17	(31.5%)	13	(22.4%)		
History of previous depressive episode	29	(53.7%)	32	(55.2%)	0.024	0.88
History of previous psychiatric disorder	7	(13.0%)	12	(20.7%)	1.185	0.28
General anxiety disorder	3		3			
Somatoform disorder	2		3			
Obsessive compulsive disorder	1		1			
Others	1		5			
Family history of psychiatric disorder	24	(44.4%)	27	(46.6%)	0.050	0.82

Paroxetine was started with at 20 mg/day, and increased to 27.6 ± 9.5 and 27.0 ± 10.0 mg/day at week 8 in the paroxetine only and paroxetine+quetiapine groups, respectively. Mean daily paroxetine doses were not significantly different between groups. The mean daily dose of quetiapine increased from 25 to about 60 mg at week 8.

Baseline HAM-A scores were similar in the paroxetine only (31.9 ± 5.5) and paroxetine+quetiapine (33.6 ± 6.5) groups. Mean HAM-A score was a few points lower in the paroxetine+quetiapine group than the paroxetine only group during the study period, but the difference between groups was not statistically significant at any time-point (Table 2, Figure 1a). The absolute decrease in HAM-A score was greater in the paroxetine+quetiapine group from Weeks 2 to 6, and also for LOCF values (all *P* values lower than 0.008) (Table 2, Figure 1b).

The baseline mean HAM-D score was higher in the paroxetine+quetiapine (28.0 ± 6.2) than the monotherapy (23.9 ± 4.8) group (Mann–Whitney *U*-test, *P* < 0.001), but due to a faster decrease in HAM-D score in the combination group, the difference between the mean HAM-D scores of groups became statistically non-significant, beginning from week 1 (Figure 2a). Adjusted mean HAM-D scores (adjusted by means of ANCOVA using baseline HAM-D score as covariate) at weeks 2–6 and also LOCF values were lower in the paroxetine+quetiapine group than the paroxetine only group (Table 3). The absolute decrease in HAM-D score was greater in the paroxetine+quetiapine group during the whole study period (Table 3, Figure 2b).

Table 2

Mean HAM-A scores and mean decrease in HAM-A scores in patients treated with paroxetine alone or in combination with quetiapine during the study period

	Paroxetine	Paroxetine + quetiapine	Z	P value ¹
HAM-A score, mean \pm SD ²				
Baseline	31.9 \pm 5.5	33.6 \pm 6.5	1.295	0.20
Week 1	24.0 \pm 10.2	22.4 \pm 7.3	1.009	0.31
Week 2	19.1 \pm 10.1	16.4 \pm 8.0	1.177	0.24
Week 4	14.3 \pm 9.7	9.8 \pm 5.4	2.103	0.035
Week 6	11.8 \pm 9.2	7.2 \pm 5.6	2.218	0.027
Week 8	7.3 \pm 8.0	5.4 \pm 4.2	0.272	0.79
LOCF ³	12.1 \pm 11.7	6.9 \pm 6.7	1.747	0.081
Decrease in HAM-A score, mean \pm SD ²				
Week 1	8.1 \pm 6.6	11.2 \pm 7.0	2.222	0.026
Week 2	12.9 \pm 7.6	17.0 \pm 7.2	2.839	0.005
Week 4	17.8 \pm 8.2	23.5 \pm 7.7	2.783	0.005
Week 6	20.1 \pm 7.5	26.0 \pm 8.4	3.148	0.002
Week 8	24.4 \pm 7.4	27.7 \pm 7.7	1.417	0.16
LOCF	19.9 \pm 10.4	26.7 \pm 8.4	3.019	0.003

¹ Calculated by Mann–Whitney *U*-test; significant *P* values (< 0.008) are denoted as *italic*.

² SD, standard deviation.

³ LOCF, last observation carried forward.

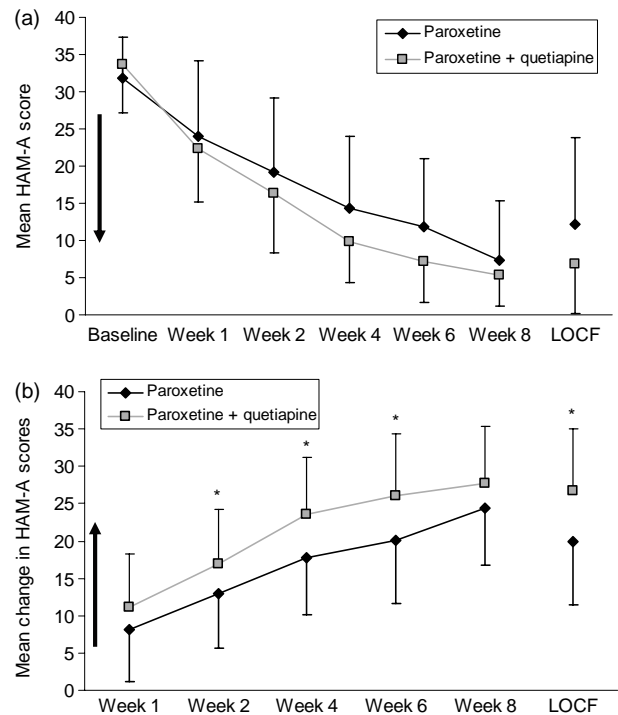


Figure 1 (a) Mean Hamilton Anxiety Scale (HAM-A) scores and (b) mean change in HAM-A scores in patients treated with paroxetine alone or in combination with quetiapine for 8 weeks. The arrow indicates the direction of improvement. LOCF, last observation carried forward. Asterisk (*) denotes *P* < 0.008.

Mean CGI Improvement score was significantly greater in the paroxetine+quetiapine group at week 4 (2.1 ± 0.9) compared to the paroxetine-only group (2.7 ± 1.2) (*P* = 0.007), but the difference between study groups was not significant at other study weeks (Table 4).

In order to differentiate ongoing depression and/or anxiety symptoms from treatment side effects, symptoms or complaints emerging after the treatment started were counted as AEs. Among the AEs, insomnia was significantly more frequent in the paroxetine only group from weeks 2 to 6; while no patients in the paroxetine+quetiapine group had insomnia, and 10.2, 8.9 and 11.9% of patients in the paroxetine only group developed insomnia at weeks 2, 4 and 6 (*P* = 0.022, 0.045 and 0.018, respectively). In the paroxetine only group, 13.3% of patients and 2.0% of those in the paroxetine+quetiapine group reported an “increase in anxiety” at week 4 which was not present before treatment (*P* = 0.048). In the paroxetine+quetiapine group, “increased appetite” was reported in 20.4% which was significantly higher than 2.4% in the paroxetine only group at week 6. There were no significant differences between groups in the frequency of other adverse events (sexual problems, retardation, sedation, agitation, dyspeptic problems, nausea, increased bowel gas, diarrhea, constipation, headache, dizziness, vertigo, tremor, excessive sweat, mouth dryness, visual acuity problems, skin rash, orthostatic hypotension,

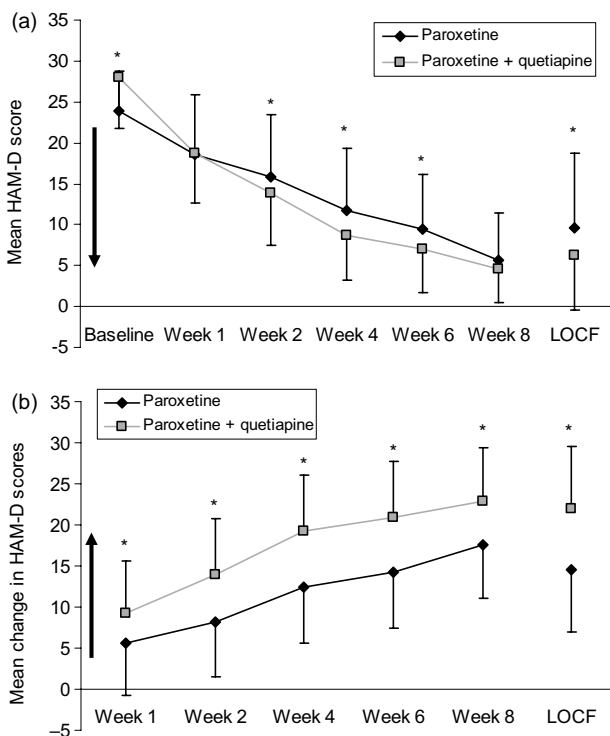


Figure 2 (a) Mean Hamilton Depression Scale (HAM-D) scores and (b) mean change in HAM-D scores in patients treated with paroxetine alone or in combination with quetiapine for 8 weeks. The arrow indicates the direction of improvement. LOCF, last observation carried forward. Asterisk (*) denotes $P < 0.008$.

amenorrhea, and cardiovascular problems). There was no significant difference in percent increase in body weight between treatment groups.

Table 3

Mean HAM-D scores and mean decrease in HAM-D scores in patients treated with paroxetine alone or in combination with quetiapine during the study period

	Paroxetine		Paroxetine + quetiapine		Test statistics ¹	P value ²
HAM-D score, mean \pm SD ³						
Baseline	23.9	± 4.8	28.0	± 6.2	$Z = 3.394$	0.001
Week 1	18.6	± 7.2	18.8	± 6.2	$F = 4.700$	0.032
Week 2	15.8	± 7.6	13.9	± 6.4	$F = 12.638$	0.001
Week 4	11.7	± 7.7	8.7	± 5.5	$F = 13.801$	< 0.001
Week 6	9.4	± 6.8	7.0	± 5.3	$F = 9.516$	0.003
Week 8	5.7	± 5.7	4.6	± 4.1	$F = 3.819$	0.054
LOCF ⁴	9.6	± 9.2	6.2	± 6.7	$F = 13.177$	< 0.001
Decrease in HAM-D score, mean \pm SD ²						
Week 1	5.6	± 5.2	9.3	± 6.3	$Z = 3.150$	0.002
Week 2	8.2	± 5.8	14.0	± 6.7	$Z = 4.357$	< 0.001
Week 4	12.4	± 6.6	19.2	± 6.8	$Z = 4.286$	< 0.001
Week 6	14.3	± 6.5	20.9	± 6.8	$Z = 3.983$	< 0.001
Week 8	17.6	± 5.8	22.9	± 6.5	$Z = 3.362$	0.001
LOCF	14.6	± 8.0	21.9	± 7.7	$Z = 4.390$	< 0.001

¹ Z values for Mann-Whitney U-test and F values for ANCOVA.

² Significant P values (< 0.008) are denoted as *italic*.

³ SD, standard deviation.

⁴ LOCF, last observation carried forward.

DISCUSSION

Antipsychotics are known to be effective in the treatment of anxious and depressive symptoms accompanying psychotic diseases.¹⁶⁻¹⁹ Atypical antipsychotics have also been reported to be effective in the treatment of major depression in non-psychotic patients when a SSRI is not effective alone.²⁶ Furthermore, Hirose and Ashby²¹ suggested that the combination of an SSRI and an atypical antipsychotic may be efficacious as an initial treatment for major depression in an open pilot study.

Due to previous studies showing the effects of atypical antipsychotics for the treatment of mixed depression and anxiety,²² we studied the effect of adding quetiapine, an atypical antipsychotic, to paroxetine treatment of patients with anxiety-associated depression.

We used scores from HAM-A which is a rating scale developed to quantify the severity of anxiety symptomatology, often used in psychotropic drug evaluation. This scale was introduced by Max Hamilton in 1959 and measures the severity of anxiety symptoms such as anxiety, tension, depressed mood, palpitations, breathing difficulties, sleep disturbances, restlessness and other physical symptoms.

We observed in our study that the decrease in HAM-A score was higher in the paroxetine+quetiapine group between weeks 2 and 6, indicating an earlier anxiolytic effect of combination therapy than with paroxetine only.

We used HAM-D and CGI improvement scores to test the antidepressant effect of addition of quetiapine to paroxetine.

HAM-D is a screening instrument designed to measure the severity of illness in adults already diagnosed as having depression.²³ It is one of the most widely used instruments for measuring outcome in mood disorders, offering high validity and reliability in measuring response to treatment.

In our study, decrease in HAM-D scores was greater in the paroxetine+quetiapine group throughout the study period. This shows that addition of quetiapine to paroxetine increases the antidepressant effect of treatment. Additionally, and similar to the other antidepressants, the therapeutic effect of paroxetine was observed in 4–6 weeks of treatment.²⁴ This may be an explanation for the significantly greater decrease in anxiety and depression scores in weeks 2–6 in the combination therapy group, but very similar scores in both groups in week 8, as a result of the effect of paroxetine in week 8. Since, in the quetiapine added group, a more rapid anxiolytic response was observed, there was no significant difference between groups at week 8 in contrast to weeks 2–6. The result of LOCF analysis was found to be significant since the scores of patients who dropped-out of the study during weeks 2–weeks were included in the LOCF analysis and the scores were significantly different between groups during weeks 2–6.

Increases in anxiety and insomnia were more prevalent in the paroxetine only group, and increased appetite and weight gain were more prevalent when quetiapine was added. These

findings are in parallel with those of other clinical studies, which have shown that short-term quetiapine treatment is associated with modest weight gain.²⁵ The increase in anxiety and insomnia in the paroxetine only group can be explained by a greater effect of paroxetine on depression than anxiety.

In conclusion, in depression associated with anxiety, when quetiapine is added to paroxetine, a more rapid anxiolytic response is observed, with a well-tolerated safety profile. Although there were limitations such as short follow-up period, no use of self-ratings and study design, which was not placebo-controlled and double-blind, this is the first study showing the benefits of adding quetiapine to paroxetine in the treatment of depression associated with anxiety. Further double-blind and placebo-controlled larger scale studies should be performed to collect more data about the long-term effects of quetiapine–paroxetine combination therapy in this group of patients.

KEY POINT

In depression associated with anxiety, when quetiapine is added to antidepressant therapy, a more rapid anxiolytic response might be possible.

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