

## ESCITALOPRAM IN THE TREATMENT OF OBSESSIVE-COMPULSIVE DISORDER: A DOUBLE BLIND PLACEBO CONTROL TRIAL

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**Background:** The tolerability and efficacy for patients with obsessive-compulsive disorder (OCD) in a large, sample on Escitalopram was studied. **Methods:** A total of 100 adults with a confirmed diagnosis of OCD were included. The percentage of patients with an adequate drug trial, defined as 42 days of continuous treatment with a serotonin- reuptake inhibitor or placebo at dosages at or above established minimal effective dosages. **Results:** Ninety-six percent of the adults who were newly diagnosed with OCD in the index year had an adequate trial of medication after their first visit for OCD. By the second half of 42 days the patient who were responding to the treatment were randomly allocated to two groups. One group received the same drug and other group was given placebo. The results were complied at the end of three months of each patient treatment. No additional psychotherapy was offered to these patients during this time period. **Conclusions:** Despite the typically chronic course of OCD, many patients with OCD responded to the Escitalopram at the dosage of twenty milligram per day.

**Key words:** Escitalopram, Obsessive Compulsive Disorder (OCD)

### INTRODUCTION

During the past decade, medications that inhibit serotonin reuptake have been found to bring about substantial improvement in 40–60% of patients with OCD.<sup>1</sup> In most patients, OCD is chronic,<sup>2,3</sup> and the sparse published data suggest that patients with OCD who discontinue medication are highly likely to experience a return or worsening of symptoms.<sup>4,5</sup>

Obsessive-Compulsive Disorder (OCD) is a chronic psychiatric disorder characterized by the presence of intrusive and unwanted obsessional thoughts and images and of compulsive behaviors.<sup>6</sup> Although many patients benefit from treatment with selective serotonin reuptake inhibitors (SSRIs), a significant proportion have limited or no response to older SSRIs and new drugs like Escitalopram may be tried. Additionally, these medicines have been associated with a slight but significant increase in onset of suicidal thoughts among adolescents being treated for depression or OCD. Cognitive behavioural therapy (CBT) may also be effective for OCD, alone or in combination with SSRIs, but there is a shortage of qualified therapists, and many patients and families cannot participate effectively in the therapy.<sup>10</sup>

We report here data on the efficacy and tolerability of a new drug Escitalopram in the pharmacotherapy for a large group of patients with OCD.

Escitalopram, the S-enantiomer of citalopram and the most selective of the selective serotonin reuptake inhibitor (SSRI) has been shown to be efficacious in the treatment of major depression. In many studies Escitalopram was significantly superior to placebo in comparisons. Citalopram was also consistently better than placebo in comparisons, except in the HAM-D-24 Anxiety/Somatization subfactor. In some comparisons with placebo,

escitalopram showed a significantly earlier onset of action or an earlier separation. Escitalopram was significantly more effective compared to placebo in treating both anxiety symptoms and the entire depression in the total depressive population, as well as in depressive patients with a high degree of anxiety.<sup>11</sup>

In another multinational, randomised, double-blind, flexible-dose study evaluated the short- and long-term antidepressant tolerability and efficacy of escitalopram and paroxetine. Tolerability was assessed by monitoring adverse events throughout the study, and discontinuation events during brief treatment interruption and tapered withdrawal. Discontinuation-emergent effects were evaluated in two separate double-blind periods. A total of 323 patients entered 8 weeks of double-blind treatment and received at least one flexible dose of escitalopram (10–20 mg/day) or paroxetine (20–40 mg/day). Patients who demonstrated evidence of a significant clinical improvement (Clinical Global Impression-Improvement of 1 or 2) at week 8 entered a 19-week, double-blind maintenance period during which they were treated with the same dose they received at week 8, followed by a 1–2-week tapered withdrawal period. A total of 89 patients (28%) withdrew during the study; significantly ( $p < 0.01$ ) more patients withdrew from the paroxetine group (34%) than from the escitalopram group (21%), and significantly ( $p < 0.05$ ) more paroxetine patients withdrew due to lack of efficacy. The mean MADRS total score improved for both treatment groups from baseline to week 8, with no statistical difference between groups. In severely depressed patients (baseline MADRS total score  $\geq 30$ ), escitalopram was superior ( $p < 0.05$ ) to paroxetine at week 27 (end of

maintenance treatment). There was a high prevalence of sexual dysfunction at baseline: the mean Arizona Sexual Experience Scale (ASEX) score was approximately 20 points in both treatment groups. Mean total ASEX scores increased slightly above baseline values during the acute period and declined slightly below baseline values towards the end of the maintenance period. During taper and cessation of treatment, patients in the paroxetine group demonstrated significantly more discontinuation symptoms relative to escitalopram based on the Discontinuation Emergent Signs and Symptoms scores.<sup>12</sup>

In another study twenty patients were enrolled, their age was  $73.0 \pm 4.8$  years. Six (30%) were women, 17 (85%) were white, 2 (10%) black, and 1 (5%) were 'others'. Seventeen (85%) of 20 patients completed the study, 3 (15%) withdrew: 1 (5%) due to lack of efficacy and 2 (10%) due to adverse events (dizziness and somnolence 1 (5%) patient each). Statistically significant improvements from baseline to end point were found with escitalopram treatment (MADRS:  $t_{19}=7.38$ ,  $p<0.001$ , effect size=2.93; HAM-A:  $t_{19}=4.19$ ,  $p<0.001$ , effect size=1.83). Significant changes from baseline in scores on 4 (Social Functioning, Role Functioning-Emotional, Mental Health, and Energy/Fatigue) of the 8 subscales of the SF-36 were also found (all,  $p<0.01$ ). In this small study in elderly patients with comorbid MDD and GAD, treatment with escitalopram 10 to 20 mg/d for 12 weeks was associated with significant improvements in symptoms of depression and anxiety.<sup>13</sup>

It is effective and generally well tolerated in the treatment of moderate to severe generalized anxiety disorder (GAD) or social anxiety disorder (SAD), panic disorder (with or without agoraphobia) as well as obsessive-compulsive disorder (OCD). Moreover, escitalopram is at least as effective as paroxetine for the treatment of GAD, SAD or OCD and appears to achieve a more rapid response than racemic citalopram in the management of panic disorder. Generally, it has a more favourable tolerability profile than paroxetine in terms of fewer discontinuation symptoms. In addition, a favourable pharmacokinetic profile permits once-daily administration of the drug. It is emphasized that additional comparative studies are required to definitively position escitalopram with respect to other SSRIs and venlafaxine. Nevertheless, available clinical data indicate that escitalopram is an effective first-line treatment option for the management of GAD, SAD, panic disorder and OCD.

There is a pressing need, then, for the development of alternative, novel treatments for OCD.

This proposal was for a 12-week, single-arm, open-label study that would evaluate safety and estimate dose in 20mg adults from 18–65 years of age, with a primary diagnosis of OCD, including those who previously have tried one or more psychopharmacologic agents with indication for OCD but who have found that treatment ineffective or poorly tolerated. It will be added to current regimen or used as sole agent. All the patients were screened for Depressive symptoms, intensity and severity of OCD and after taking the written informed consent. These 100 subjects will participated in a double-blind, placebo-controlled 12-week trial of Escitalopram as a sole agent for their currently inadequate therapy.

## MATERIAL AND METHODS

This study was continued for 12 weeks and comprised of two phases. Phase 1 was an open label in which all participants will receive daily escitalopram for six weeks. Those who have responded to treatment at the end of the six weeks were randomly assigned to either continue or discontinue with escitalopram and switched to placebo for their treatment for additional six weeks. Those who do not respond to treatment at the end of phase 1 will discontinue the study and be offered three visits with the study clinician or referred elsewhere for treatment, based on their preference. Study visits are made at baseline, and at weeks 1, 2, 4, and 6 in phase 1 and weeks 7, 9, 11 and 12 in phase 2.

### Eligibility

Age eligible for study: 18 years and above,  
Sex eligible for study: Both sexes

### Inclusion Criteria

1. Diagnosis of OCD
2. A minimum score of 60–120 on the PADUA inventory for Obsessive Compulsive Disorder scale<sup>7</sup> at both the screening and baseline visits

### Exclusion Criteria

1. Life time history of psychosis or cognitive dysfunction due to a general medical condition or substance use
2. A primary diagnosis of another axis 1 psychiatric disorder
3. Alcohol or other substance abuse or dependence within the last six months
4. Unstable medical condition
5. Clinically significant laboratory abnormality
6. Failure of previous 10 week trail of escitalopram of at least 20 mg
7. Active Suicidality
8. History of violent behaviour in the past year or current risk of serious violence
9. History of sensitivity to escitalopram

10. Use of other investigational drugs within 30 days of baseline or other psychoactive drugs or herbs within 14 days of baseline (28 days for fluoxetine)
11. Need for concurrent psychotherapeutic intervention
12. Pregnancy or lactational women

Doctors trained by the investigators saw the patient in out patient or in-patient departments and then referred to the investigators if felt that they are suffering from OCD. The investigators evaluated all these referred cases and made clinical diagnoses using diagnostic checklists similar to the criteria for OCD given in the Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition (DSM-IV).<sup>7</sup>

Patients with definite OCD symptoms of either obsessions or compulsions or both, as listed in the PADUA inventory,<sup>8</sup> were then screened and documentation completed. This documentation included the written informed consent which was obtained after explaining to the patient all the procedures including the randomisation process at the end of phase one and possibility of their being included into the placebo group. These patients were then given the demographic proforma which was in a semi structured form to take various details. These patients also were given Beck Depression inventory to see the co morbid depression. All of them were assessed for symptoms and intensity and severity of OCD by PADUA scale, translated and validated in Urdu. The cut off values on PADUA inventory were for mild cases the score of 60–119, moderate case 120–179 and sever case 180–240 was acceptable. Only sever form of OCD cases were included in the study. They were assessed for their disability by the Sheehan's disability rating scale. The assessment included for the symptoms causing marked distress, occupied at least one hour per day, or significantly interfered with the patient's role functioning, normal routine or social activities.

All patients in the first phase of the trial were given Escitalopram 10 mg per day in the beginning and after three weeks if required the dosage was increased to twenty mg per day. These medications were in a loose form provided by the company and the placebo tablets were also exactly of the same size, color and shape. The placebo were especially made by the pharmaceutical company and it was ensured that the tablets provided to the patient either the Escitalopram or the placebo were exactly of the same quality in all respects of appearance. These drugs were dispensed by a person who had an experience with the pharmacy. The raters and investigators were absolutely blind to the information about the drugs dispensing. This was also ensured that the dosage escalation was also not done by the

raters and all the patient were assessed by a psychiatrist independent of the raters in during the trail period for the dosage requirements as well. This process made the procedure bit complicated but this was carried out to rule out any bias in the study.

The assessments after the six weeks were submitted by the raters to the consultant's psychiatrists involved in the study but not clinical active in the treatment of the patients in any form. After the end of six weeks trial period all the patients who were responders according to the assessments of the consultant psychiatrist were divided into two groups. One of the groups was continued to have the Escitalopram and the other group was given the placebo tablets. Again the raters were blind to the distribution of the groups. These patients were assessed by the raters at the end of 7, 9, 10 and 12 weeks period.

The results were analysed on the computers for the intensity and severity of OCD and its improvements over the period of time. The relapse in depression after the patients were replaced with placebo was also recorded and analysed. The intensity and severity of symptoms of OCD for all patients on Escitalopram and later on if on Escitalopram or placebo was also assessed on the computers.

## RESULTS

Of the OCD patients in trial care, 57.1% of females and 42.9% of male had at least 10 mg of adequate pharmacotherapy of Escitalopram (Figure-1 and 2). Mean age was 37 years with range of 16–58 years. Majority of the patients received between 15–20 mg of Escitalopram. This dosage escalation was carried out by the investigators other than the one who are involved in the evaluation and scoring of the patients. The dosage was clinically based on the basis of intensity and severity of the symptoms on follow up visits. If the patient is not responding or partially responding on the specific dosage the escalation was done. The patients who were not responding at all were given the maximum dosage and at the end of six weeks labelled as non responders group.

For adults, the odds of responding to medication were significantly higher in patients with more severe OCD (odds ratio= 13.44, Wald's  $\geq 2 = 28.80$ ,  $p = 0.0001$ ), patients with shorter history of six months to one year and had less number of anti-obsessional drugs responded better (odds ratio= 3.21, Wald's  $\geq 2 = 4.64$ ,  $p = 0.03$ ) (versus patients having more anti-obsessional drug trails and history of more than a year (odds ratio= 3.76, Wald's  $\geq 2 = 5.75$ ,  $p = 0.02$ ), and patients with a comorbid depressive disorder (odds ratio= 2.53, Wald's  $\geq 2 = 12.234$ ,  $p = 0.0004$ ). The odds of treatment were not significantly related to sex, age, or

presence of a psychiatric comorbidity other than depression. When the variable OCD time frame of illness was removed from the model, patient with PADUA scores of 180 or more (odds ratio= 2.86, Wald's  $\geq 2 = 4.27, p = 0.04$ ) and comorbid depressive condition (odds ratio= 2.07, Wald's  $\geq 2 = 9.23, p = 0.002$ ) remained significantly related to the receiving 20 mg of Escitalopram medication.

Around 6% of diagnosed cases dropped out of the study among these the primary reasons for the discontinuation of trial was dissatisfaction in (28%), preferred treatment with behavioural therapy alone (22%), refusal of medication (16%), and miscellaneous other reasons (24%). No reason could be ascertained for 10% of the patients dropped out from study.

The prospectively defined primary analysis of efficacy was time to relapse from the start of the double-blind treatment, with relapse defined as an increase in the PADUA total score of 20–60 points or greater, or a lack of efficacy as judged by the investigator.

Of the 100 patients who entered the initial acute treatment trial, 94 completed, and the 68 responded to escitalopram entered randomization to placebo (n=34) or escitalopram (n=34) 10/20 mg. Of these, all completed the 12-week, randomisation, placebo stage.

All efficacy analyses at this stage were based on the intention-to-treat (ITT) population. To exclude potentially confounding effects, the influence of discontinuation symptoms on the primary analysis was investigated by censoring relapses occurring during the first 7 and 14 days after randomisation.

With a mean PADUA score of 76, these patients had moderate to severe OCD. Their mean baseline total score of 152 also defined their clinical-obsessive behaviour, and they were a markedly ill population (Sheehan's disability score, 5) with low levels of co morbid depression (Beck depression scale total score, 10).

In the randomisation phase, there were no significant differences in the demographic and clinical parameters between the 2 treatment groups.

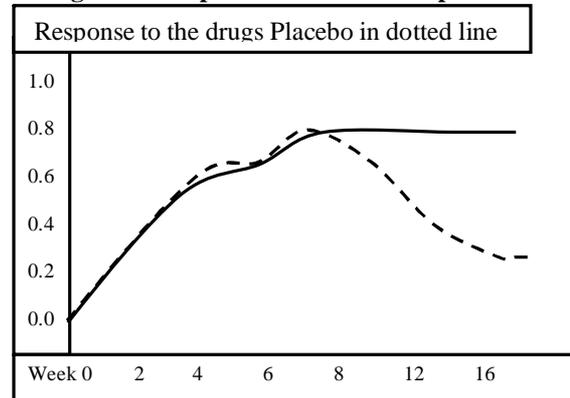
The primary efficacy analysis demonstrated a significantly superior effect over placebo of escitalopram for time to relapse of OCD ( $p < 0.001$ ). The proportion of patients who relapsed were significantly higher in the placebo group than in the escitalopram group (52% vs 24%, respectively;  $p < 0.001$ ).

Cox proportional analysis indicated a significant hazard ratio of 2.74 ( $p < 0.001$ ) towards benefit from escitalopram. This was significant from week 4 ( $p < 0.05$ ), and was maintained throughout the 12 weeks of the trial.

Following 6 withdrawals from the original 100 patients with OCD, a further 2% (2 patients) withdrew from this placebo trial stage in the placebo and escitalopram groups.

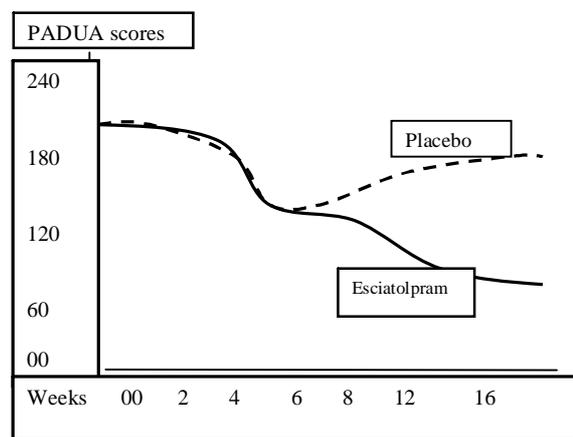
While 70.5% of the acute-phase patients had treatment-emergent adverse events (AEs), this was reduced for both placebo and escitalopram groups in the second stage both during the first 2 weeks from randomization (29.8% vs 14.1%, respectively) and from week 2 to 16 (31.8% vs 39.3%). The former of these was significantly lower in the escitalopram group ( $p < 0.001$ ), with this difference arising more specifically from escitalopram-associated reductions in nausea (5.7% vs 0.6%,  $p < 0.01$ ) and dizziness (15.9% vs 0.6%). However, these significant differences disappeared from week 2 to 6. There were no clinically relevant changes within or differences between the vital signs of these 2 treatment groups.

Figure-1: Response rate of Escitalopram Vs



Placebo over the 16 weeks period

Figure-2: Initial Escitalopram after six weeks



randomised, Dotted line on Placebo

This was indicated that patients that remained on escitalopram remained well for longer than did those who were switched to, double-blind, to

placebo. This, we noted, indicated that patients who remain on escitalopram have significantly improved outcomes and prevent symptoms reoccurrence.

## DISCUSSION

In this trail of locally made escitalopram (Esciatolpram) the dosage of the drug in most of the patients had to be around 20 mg per day to have adequate and significant drops in the PADUA scores. The drug escalation required another couple of weeks so that the initial time period was, although included in the study period, however showed less significant results than if the time period for the study if it would have been increased. In our opinion more time to trail the Esciatolpram would have been able to generate more promising results.

The majority of the patients at the end of six weeks showed responses but if they are complimented by the psychotherapeutic interventions could have brought more significant results as well.

The detail assessment of the PADUA scores highlighting the reduction in the symptoms of OCD either in obsessions and or compulsions would be able to show which domains were more affected and helpful in treatment either any specific obsessions or compulsions.

Comorbid depression may have motivated adult patients to persist with SRI treatment (perhaps aiming at their depressive rather than OCD symptoms) or may have motivated prescribing psychiatrists to more vigorously pursue medication trials aimed at one or both disorders.<sup>8</sup> Our data do not allow us to distinguish between these possibilities.

Contrary to our hypothesis, the odds of adequate medication were not related to sex, the presence of psychiatric conditions other than depression, or the number of visits per week for these conditions. Thus, men and women were equally interested in receiving drugs for OCD, and co morbid psychiatric conditions.<sup>9</sup> Since many patients in this study see more than one provider over the lengths of time we studied, an analysis of provider characteristics was not feasible.

Newly diagnosed patients with a co morbid psychiatric condition other than depression were less likely to respond to medication, these co morbidities may affect compliance or may dissuade patients or clinicians from adding yet another medication to a patient's regimen. These possibilities deserve further study.<sup>12</sup>

Future research should investigate the application of both apparently effective and innovative methods with OCD patients and their treating clinicians. Both patient-related and physician-related sources of inadequate treatment deserve study.<sup>6,7</sup>

Like many patients with mood disorders reported in other studies, a substantial minority of patients with OCD diagnosed in this trial were not enjoying the benefits of available psychotherapeutic interventions, either in the short term or the long term.

One limitation of this study was the duration of acute therapy. Both large national surveys and pharmacotherapy studies with other SSRI's indicate that OCD may require a fairly lengthy acute treatment (in excess of 12 weeks) before maximum improvement of symptoms is achieved. In this study, the statistically significant continued improvement in OCD symptoms (measured by the PADUA scale) after 6 and 12 weeks of acute therapy suggests that the full therapeutic effect of Esciatolpram on the improvement of OCD symptoms may not have been observed even after 9 months of therapy.

## CONCLUSION

The Esciatolpram is having clinically significant efficacy in the treatment of OCD with or without depressive symptoms. This drug has side effects profile relatively much better than the other SSRI's and is also well tolerated in the longer period.

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**Funding Information:** Nabi Qasim Pharmaceuticals Pakistan Pvt. Ltd has supported this study.

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