Original Article

# Benzodiazepine as an Adjuvant in Management of Depression

**Girish K and Moulya Nagraj***

Department of Pharmacology, Kempe Gowda Institute of Medical Sciences, Bangalore - 560070, India

**Address for Correspondence**

Department of Pharmacology, Kempe Gowda Institute of Medical Sciences, Bangalore - 560070, India.
**E-mail:** moulyanagraj@gmail.com

## ABSTRACT

**Objective:** To assess the effects of benzodiazepines in management of depression.
**Methodology:** An open label 8 week study of escitalopram with or without benzodiazepines in moderate to severe depression. 30 subjects willing to give written informed consent, fulfilling the inclusion, exclusion criteria were included in the study and grouped into escitalopram alone or escitalopram with benzodiazepines.
**Results:** In the study 60% of the subjects were prescribed benzodiazepines, i.e. clonazepam. Though escitalopram with clonazepam had faster onset of action in controlling depressive symptoms than escitalopram alone, there was no significant difference in the pattern of reduction of MADRS score in both the groups.
**Conclusion:** Benzodiazepines as adjuvant to antidepressants are commonly used in management of depression, but benefits of combination are unclear.

**Keywords**: Depression, Escitalopram, Clonazepam, MADRS score.

## INTRODUCTION

Depression is the most common chronic mood disorder affecting one's mood, feelings, behavior, thoughts and also physical health.[1] Frequently anxiety co-occurs with depression and depressed individual differ in respect to clinical features, severity and course of illness and also their response to drug therapy.[2,3] Benzodiazepines are commonly used empirically as adjuvant with antidepressants in the management of depression to control anxiety and sleep disturbances.

Several classes of effective antidepressants are available and among SSRIs, Escitalopram is generally preferred drug as primary option because of their high efficacy, safety and tolerability with least chances of mood fluctuations.[4] Anti-depressants are effective for both symptoms of depression and for coexisting anxiety. However, therapeutic responses to antidepressants often do not occur for several weeks and benzodiazepines are commonly prescribed for more immediate

symptom relief.[5] Although benzodiazepines are used commonly, the benefits of combining benzodiazepines to anti-depressant therapy in depression are indistinct. Hence the present study was taken up.

## OBJECTIVES

To assess the benefits of benzodiazepines as adjuvant to anti-depressants in depression.

## METHODOLOGY

An open label, parallel group, 8 week study of escitalopram with or without benzodiazepines in moderate to severe depression. The study was conducted in the Department of Psychiatry, Kempegowda Institute of Medical Sciences & Research Center, Bangalore, between January 2013 and April 2014.

The study included 30 subjects who were diagnosed with moderate to severe depression as per International Classification of Diseases (ICD-10). A written informed consent was obtained from all the study subjects after fully explaining the study procedure to their satisfaction, in both English and vernacular language.

Subjects of either sex aged between 18-65 years, with first episode or recurrent episode of depression according to (ICD-10) with baseline score >18 and < 40 according to Montgomery-Åsberg Depression Rating Scale (MADRS)and willingness to give written informed consent and available for follow up were included.

Exclusion Criteria were, subjects with severe depression requiring ECT with high risk of suicidal tendency, atypical depression, depression secondary to medical illnesses, post-traumatic depression, postpartum depression, pregnant women, breast feeding and women planning to conceive, previous history of epilepsy, sexual dysfunction, serious or uncontrolled medical illness like glaucoma, hypertension, diabetes mellitus, hyperlipidemia, myocardial infarction, hepatic and renal impairment, known history of allergy to both the study medications and participation in any other research study in recent past.

After obtaining approval and clearance from the institutional ethics committee 30 subjects who met the inclusion and exclusion criteria were included in the study. Anonymity, confidentiality and professional secrecy was maintained for all the study subjects. This study was conducted according to the ICH-GCP guidelines and the revised Declaration of Helsinki.

30 subjects diagnosed with moderate to severe depression were included in the study. Subjects were prescribed escitalopram 10mg once daily after food, which may be further increased by 5mg if necessary after 2 weeks upto a maximum of 20 mg daily, or escitalopram with benzodiazepines. The subjects were grouped into escitalopram alone or escitalopram with benzodiazepines. Clinical improvement was assessed by using MADRS, at baseline and after 4 weeks (visit 1), and 8 weeks (visit 2). Reduction of MADRS score to < 12, were considered remitters and 50% reduction from baseline scores were considered responders. Vitals like pulse, blood pressure, height and weight were assessed, and monitored for any adverse reactions during clinical examination at each visit.

The subjects follow up was based on OPD or by telephonic conversation with a buffer of 1 week of the allotted follow up date. Three attempts per patient were made at different intervals for those who failed to follow up and subjects who were not reachable by telephone even after 3 attempts on different days were declared as lost to follow up.

## RESULTS

In the present study escitalopram alone or benzodiazepine as adjuvant were prescribed, for the management of depression. Among the benzodiazepine sublingual clonazepam 0.25mg was prescribed and increased to 0.5 mg if necessary, suggesting that clonazepam is most commonly used and combined with antidepressant. Of the 30 study subjects fulfilling the inclusion and exclusion criteria n=12(40%) were prescribed escitalopram alone and subjects n=18(60%) with escitalopram and clonazepam. Subjects (n=29) completed the study duration and 1 subject was lost to follow up, in escitalopram combined with clonazepam group. The mean age was 35 years, majority were between 26-35 years, indicating a peak occurrence in 2nd and 3rd decades of life. The female: male ratio was 2:1 and urban: rural was 22:8 and married: unmarried ratio was 5:1 indicating urban preponderance with an influence of lifestyle and increased awareness of the illness (Table 1). Most of the subjects belonged to upper middle socioeconomic strata with few having positive family history of depression (n=1) and previous history of depression (n=3). In 8 subjects of age group > 40 years had co-morbid illness like diabetes and hypertension. The comorbid illnesses were well controlled with appropriate antidiabetic and antihypertensive agents.

The findings of general physical examination were within normal limits in the study subjects and baseline characteristics showed no clinical significance between the study groups at the entry of study period. In both the groups there was no significant difference in the findings of general physical examination from baseline to visit 2.

Majority of the subjects were moderately depressed by MADRS score (Table 2) at baseline with no significant difference (p=0.298) between the study groups. The objective in reduction of MADRS score from baseline to visit 2 was statistically significant within the groups but there was no significant difference between the groups (Figure 1). Reduction in severity of inner tension and insomnia were similar in both group indicating that addition of clonazepam had no added advantage. At visit 1 responders were (n=13, 72%) and remitters (n=6, 33%) in escitalopram combined with clonazepam and responders (n =3, 25%) and remitters (n=2, 16.6%) in escitalopram alone group. At visit 2 number of responders and remitters (n=18, 100%) in escitalopram combined with clonazepam group and responders and remitters (n= 10, 83.3%) in escitalopram alone group (Table 3). From above observation it suggests that escitalopram with clonazepam has faster onset of action and is more effective in controlling depressive symptoms than escitalopram alone.

In both the study groups, baseline laboratory parameters were within normal limits. Though the study drugs were well tolerable, few subjects complained of drowsiness (n=2), increased sleep (n=1) less frequently.

## DISCUSSION

In the study 60% of the subjects were prescribed benzodiazepines, for various reasons like early symptom relief, to relieve anxiety and to improve sleep. Based on the observations in the study escitalopram with clonazepam has faster onset of action with better control of depressive symptoms than escitalopram alone but at visit 2 there was no significant difference in the pattern of reduction of MADRS score between the groups. Few studies suggested that clonazepam has antidepressant effect when used for short term, although this benefit is unclear on long term.[6] A meta-analysis showed that

premature discontinuation of treatment was less in subjects receiving combination therapy when compared to subjects on antidepressants alone, and also subjects receiving combination therapy had improvements in symptoms faster.[7] This permits for further long term studies to know the advantage of combining benzodiazepines with antidepressants in the management of depression.

Limitations of the study were, it was an open label, shorter duration of follow up, sample size was small and hence might not be enough to identify the minute differences in efficacy parameters and adverse events between the study groups.

## CONCLUSION

Even though benzodiazepines is commonly prescribed as adjuvants, its benifits are indistinct in management of depression and therefore it should be used judiciously to balance against the risks like development of dependence, tolerance, accident proneness, teratogenicity and costs.

## ACKNOWLEDGEMENT

The authors are grateful for the support of Psychiatry Department, KIMS Bangalore, Clinical Pharmacology Unit, KIMS Bangalore, and Department of Pharmacology, KIMS Bangalore.

## REFERENCES

1. National Collaborating Centre for Mental Health: The Nice Guideline on the Treatment and Management of Depression in Adults. *The British Psychological Society and The Royal College of Psychiatrists.* [Serial online] 2010 Oct [cited 2014 Jun 19] Available from: URL:http://www.nice.org.uk/nicemedia /live/12329/45896/45896.pdf
2. Debjit B, Kumar K.P. S, Shweta S, Sharvan P, Sankar D A. Depression-symptoms, causes, medications and therapies. *The pharma journal*. 2012; 1(3):37-48
3. Beekman ATF, Anton EB, van Balkom JLM, Deeg DJH, van Dyck R, van Tilburg W. Anxiety and depression in later life: co-occurrence and communality of risk factors. *Am J Psychiatry*. 2000; 157:89–95
4. O'Donnel JM. Shelton RC. Hypnotics and Sedatives. In: Brunton LL, Chabner BA, Knollmann BC, eds. Goodman & Gilman's: The Pharmacological Basis of Therapeutics. 12th edition. New York. McGraw-Hill; 2011:607-629.
5. Berk M. Selective serotonin reuptake inhibitors in mixed anxiety-depression. *Int Clin Psycho pharmacol.* 2000; 15(2):S41–S45.
6. Londborg PD, Smith WT, Glaudin V, Painter JR. Short-term cotherapy with clonazepam and fluoxetine: anxiety, sleep disturbance and core symptoms of depression. *J Affect Disord* 2000; 61:73–79.
7. Furukawa TA, Streiner DL, Young LT. Antidepressant and benzodiazepine for major depression. *Cochrane Database Syst Rev.* 2002; 1:CD00026.

**Table 1.** Demographic details and baseline characteristics

| | Escitalopram | Combined with benzodiazepines |
|---|---|---|
| Age | 35.7931±12.36752 | 35.28±12.28 |
| Male | 3(25%) | 7(38.8%) |
| Female | 9(75%) | 11(61.1%) |
| **Marital status** | | |
| Married | 9(75%) | 13(72.2%) |
| Unmarried | 3(25%) | 5(27.7%) |
| **Residence** | | |
| Urban | 10(83.3%) | 15(83.3%) |
| Rural | 2(16.6%) | 3(16.6%) |
| Weight | 62.37931±6.526943 | 62.32±6.63 |
| Pulse | 76.75±5.61 | 77.5±4.63 |
| Systolic blood pressure | 123.44±10.54 | 123.21±10.65 |
| Diastolic blood pressure | 79.10±8.47 | 79.07±8.63 |
| MADRS baseline | 29.58±5.22 | 29.96±5.39 |

**Table 2.** Grading of MADRS score

| Score | Grading |
|---|---|
| 7 to 19 | Mild depression |
| 20 to 34 | Moderate depression |
| 35 to 60 | Severe depression |

**Table 3.** Number of responders and remitters

| Outcome | Visit 1 | |
|---|---|---|
| | Escitalopram | Combined with Benzodiazepines |
| Responders | 3(25%) | 13 (72.2%) |
| Remitters | 2(16.6%) | 6(33.3%) |
| | **Visit 2** | |
| Responders | 10(83.3%) | 18(100%) |
| Remitters | 10(83.3%) | 18(100%) |

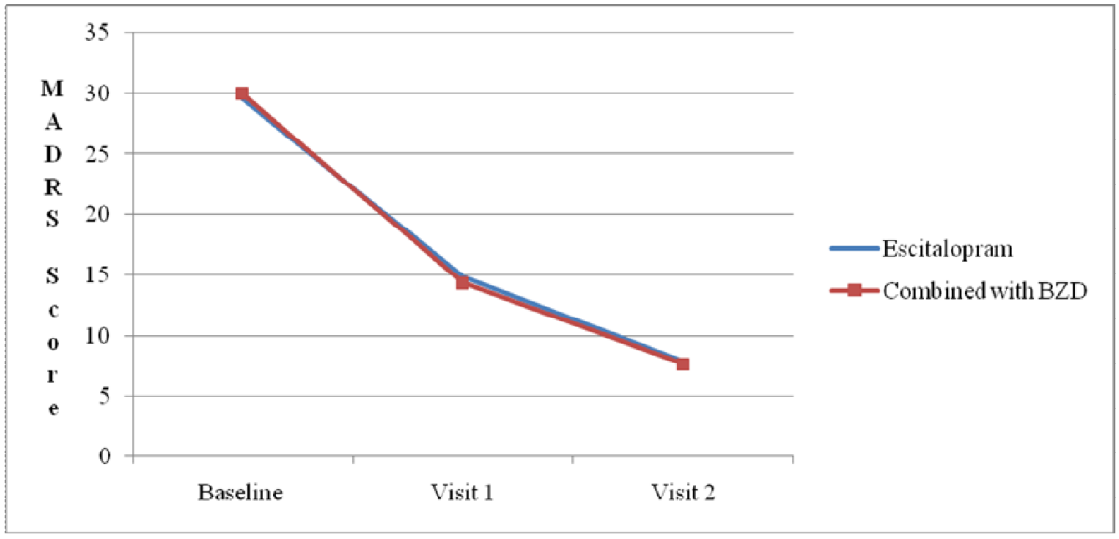


**Figure 1.** Montgomery-Åsberg Depression Rating Scale score at each visit