International Journal of Research in Medical Sciences
Dar SA et al. Int J Res Med Sci. 2018 Jun;6(6):2081-2085
www.msjonline.org
pISSN 2320-6071 | eISSN 2320-6012
DOI: http://dx.doi.org/10.18203/2320-6012.ijrms20182293

Original Research Article

Addition of benzodiazepines to selective serotonin reuptake inhibitors to optimize treatment of depression: a hospital based study

S. A. Dar*, B. A. Bhat, M. M. Jan

Departments of Psychiatry, Government Medical College Srinagar, Srinagar, Jammu and Kashmir, India

Received: 29 March 2018
Accepted: 27 April 2018

***Correspondence:**
Dr. Shabir Ahmad Dar,
E-mail: Shabir1055@gmail.com

ABSTRACT

Background: Selective serotonin reuptake inhibitors ameliorate depression and anxiety slowly and in fact increase anxiety or insomnia initially. Addition of clonazepam to escitalopram improves response: thereby improving symptoms associated with depression, reducing side-effects and alleviating core depressive symptoms. The aim of study was to assess the benefits of adding benzodiazepines in management of depression.
Methods: It was an open label prospective study of 8 weeks of escitalopram group versus escitalopram with benzodiazepine group in moderate to severe depression. 51 subjects who gave written informed consent and were fulfilling the inclusion and exclusion criteria were included in the study and grouped into escitalopram alone or escitalopram with benzodiazepines.
Results: In the present study nearly 60% of the patients were prescribed clonazepam. Though combined group with benzodiazepines had faster onset of action in controlling depressive symptoms than escitalopram group alone at 4 weeks of treatment, there was no significant difference in the pattern of reduction of MADRS score in both the groups at 8 weeks of follow up.
Conclusions: Augmenting benzodiazepines to antidepressants are more effective in management of depression associated anxiety and sleep disturbances initially till SSRIs start action.

Keywords: Clonazepam, Depression, Escitalopram, MADRS score

INTRODUCTION

Depression is the commonest mood disorder affecting one's mood, feelings, behavior, thoughts and physical health.[1] Central to it, is depressed mood and/or loss of pleasure in most activities. Severity of the disorder is determined by the number and severity of symptoms, as well as the degree of functional impairment. A formal diagnosis using the ICD-10 classification system requires at least four out of ten depressive symptoms, whereas the DSM-IV system requires at least five out of nine for a diagnosis of major depression. Symptoms should be present for at least 2 weeks and each symptom should be present at sufficient severity for most of every day. Both diagnostic systems require at least one (DSM-IV) or two (ICD-10) key symptoms (low mood, loss of interest and pleasure or loss of energy to be present.[2,3]

People with depressed mood are usually sad, anxious, or empty; they may also feel notably hopeless, helpless, dejected, or worthless. Other expressed symptoms may include senses of guilt, irritability, or anger.[4] The presence of an anxiety disorder also significantly increases the risk for suicidal ideation and suicide attempts.[5,6] Expressed insomnia, excessive sleeping, fatigue, and vocalizing general aches, pains, and digestive problems and a reduced energy may also be present in individuals experiencing depression.[7]

Benzodiazepines are mostly used as add on with antidepressants in the treatment of depression to improve anxiety and disturbed sleep. Among SSRIs, escitalopram is preferred drug because of its high efficacy, safety and tolerability with least chances of mood fluctuations.[8]

SSRIs are the first-line medications in the management of various anxiety and depressive disorders. Antidepressants are effective for symptoms of depression and coexisting anxiety in part because of their established efficacy, their broad spectrum of activity, good tolerability profile, efficacy for co morbid depression, and suitability for long-term use, in keeping with treatment recommendations for these generally chronic conditions.[9] The primary limitations of SSRIs is the time to start action, the risk of agitation and anxiety at the initiation of treatment.[9-13] These factors may contribute to reduced adherence to treatment and poorer outcomes. Benzodiazepines are commonly prescribed for more immediate symptom relief.[14] Although benzodiazepines are used commonly; the benefits of combining benzodiazepines to an antidepressant therapy in depression are indistinct. Hence the present study was taken up.

METHODS

This study was age matched 8 week, prospective, open label of Escitalopram with or without benzodiazepine group in patients of moderate to severe depression. It was conducted from June 2015 through November 2015 after seeking permission from the departmental ethical committee. Patients both males and females between 18 to 60 years of age attending both in and outpatient unit of Government Psychiatric Diseases Hospital, Srinagar, Kashmir, India with diagnoses of moderate to severe depression as per ICD 10 criteria, either first episode or recurrent episodes with baseline score >18 and <40 according on Montgomery-Åsberg Depression Rating Scale (MADRS) and available for follow up were enrolled in the study. A written informed consent was taken from each patient in locally understandable language and was given freedom of choice to accept or refuse participation in the study. As a result of which 63 patients were included in the study. Detailed history, physical examination and relevant investigations were done before screening for any psychiatric diagnosis. Physical illnesses like hypertension, diabeties millitus, chronic obstructive pulmonary disease if any were well controlled with appropriate medications.

Each participant was prescribed escitalopram10mg once daily after food, which was further increased by 5mg if necessary after 2 weeks with a maximum of 20mg daily, or Escitalopram with benzodiazepines. Mouth dissolving clonazepam 0.25mg was prescribed and increased to 0.5mg if necessary. The subjects were grouped into escitalopram alone or escitalopram with benzodiazepines groups. Clinical improvement was assessed by using MADRS at baseline, 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. The Montgomery-Åsberg Depression Rating Scale (MADRS) is a 10-item clinician administered scale, designed to be particularly sensitive to antidepressant treatment effects in patients with major depression.[15] All of the cases were interviewed for socio-demographic parameters like age, gender, marital status and MADRS at baseline, visit 1 and 2.

RESULTS

During the 6 months study period, a total of 63 patients who were diagnosed with moderate to severe depression from the department of psychiatry were enrolled as per our inclusion and exclusion criteria. However out of these enrolled patients 05 patient lost the follow up at visit 1and 7 patients lost the follow up on visit 2 hence were excluded from the study (Table 1).

Table 1: Socio-demographic characteristics of escitalopram group and combined group with benzodiazepines.

Socio-demographic characteristics	Escitalopram group	Combined group with benzodiazepines
Age	36.7 6±10.36	36.48±10.28
Male:Female	7:14	10:20
Rural:Urban	3:18	4:26
Married:Unmarried	16:05	22:08

At week 4 that's visit 1, patients receiving combined group with benzodiazepines achieved a clinical response (i.e., ≥ 50% reduction from baseline in MADRS score). A total of 85% of these Responders also achieved remission (i.e., a MADRS score ≤12). Rates of response and remission associated with combined group with benzodiazepines was significantly higher than those in Escitalopram group and the difference was statistically significant (p value <0.0001) (T able 2).

DISCUSSION

The main widely accepted reason for use of benzodiazepines in the treatment of anxiety and

depression is for short-term use to improve symptom relief at the beginning of therapy, with subsequent tapering on follow up, when the SSRI begins to exert an effect.[16.17] Both anxiety and depression appear to have distinct as well as shared patho-physiologic mechanisms.[18] Since, there are high rates of discontinuation with initial SSRI therapy, rapid symptom relief may improve adherence to antidepressant medication, which may ultimately improve overall outcomes.[19]

Table 2: Number of responders and remitters in escitalopram group and combined group with benzodiazepines and individual MADRS score in each group.

Baseline	Escitalpram group	Combined group with benzodiazepines	MADRS score Escitalopram group	MADRS score combined group with benzodiazepines	P value
	n=21	n=30	30.44±5.36	30.74±5.40	0.85
Outcome	Visit 1				
Groups	Escitalpram	Combined group with benzodiazepines	MADRS score escitalopram group	MADRS score combined group with benzodiazepines	P value
Responders	10	26	18.26±2.66	14.72±2.36	<0.0001*
Remitters	04	08			
Visit 2					
Responders	18	28	13.66±2.42	13.86±2.32	0.77
Remitters	16	26			

Adding of a benzodiazepine to an SSRI can provide more rapid symptom relief in depression and more rapid stabilization of panic or social phobia symptoms than the SSRI alone.[20-23] Benzodiazepines are not recommended as monotherapy in depression, as they primarily improve the symptoms of insomnia and restlessness, rather than the core depressive symptoms of sadness, anhedonia, and low energy.[24]

In our study the mean age was 36 years, majority of participants were between 26-35 years, indicating a peak occurrence in 2nd and 3rd decades of life. The female: male ratio was 2:1 which is in concordance with the fact that the prevalence of major depression is higher in women than in men. one explanation of the rise and fall of the female/male ratio over the life cycle could be that female sex hormones might contribute to the higher female rates. However, social roles-especially marital and employment status-are also changing over the life cycle.[25] Urban preponderance can be explained with an influence of lifestyle and increased awareness of the illness in urban areas.

In the study around 60% of the subjects were prescribed benzodiazepines, for various reasons like early symptom relief, to relieve anxiety and to improve sleep and it was slowly tapered off. 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. Similar study results have been seen by Pollack et al, done on Paroxetine in panic disorder.[26]

Few studies suggested that Clonazepam has antidepressant effect when used for short term, although this benefit is unclear on long term.[27] 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.[28] Depression often presents with anxiety. The rate of anxiety comorbidity among patients with depression varies between 33% to 85%.[29]

Combination prescriptions appear to be common in many parts of the world. For example, a multi-centre study in Japan found that approximately 60% of the first visit psychiatric patients with major depression were prescribed benzodiazepines in addition to antidepressants.[28]In France, a general population survey revealed that slightly less than two thirds of anti depressant users were also prescribed benzodiazepines (anxiolytic or hypnotic) concomitantly.[30] Gradual taper of long-half life benzodiazepines appear to increase the rate of successful discontinuation.[31] Difficulty in tapering, with more pronounced withdrawal symptoms, does not seem to predict inability to successfully complete the taper. Psychological support, appears to be a critical factor in this process.[32]

Most, information indicates that treatment with benzodiazepines for at least, a few weeks is needed before withdrawal is generally a serious concern, and that, withdrawal is most, likely to occur when shorter-acting agents are stopped abruptly. Taper regimens have been described to lessen the difficulty in discontinuing benzodiazepine therapy.[33]

CONCLUSION

We conclude with the message that Benzodiazepines as add on therapy to antidepressants are more effective in

management of depression associated anxiety and sleep disturbances initially till SSRIs start action.

Funding: No funding sources
Conflict of interest: None declared
Ethical approval: The study was approved by the Institutional Ethics Committee

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. 2010. Available from: URL:http://www.nice.org.uk/nicemedia/live/12329/45896/45896.pdf.
2. World Health Organization. The ICD-10 classification of mental and behavioural disorders: clinical descriptions and diagnostic guidelines. World Health Organization; 1992. American Psychiatric Association, American Psychiatric Association. DSM-IV-TR: Diagnostic and statistical manual of mental disorders, text revision. Washington, DC: American Psychiatric Association. 2000;75:78-85.
3. World Health Organization. The ICD-10 classification of mental and behavioural disorders: clinical descriptions and diagnostic guidelines. World Health Organization;1992.
4. Thapar A, Collishaw S, Pine DS, Thapar AK. Depression in adolescence. Lancet. 2012 Mar 17;379(9820):1056-67.
5. Sareen J, Cox BJ, Afifi TO, de Graaf R, Asmundson GJ, ten Have M, et al. Anxiety disorders and risk for suicidal ideation and suicide attempts: a population-based longitudinal study of adults. Archives of general psychiatry. 2005 Nov 1;62(11):1249-57.
6. Bolton JM, Cox BJ, Afifi TO, Enns MW, Bienvenu OJ, Sareen J. Anxiety disorders and risk for suicide attempts: findings from the Baltimore Epidemiologic Catchment area follow-up study. Depression and Anxiety. 2008 Jun 1;25(6):477-81.
7. National Institute of Mental Health. Depression. Available at: https://www.nimh.nih.gov/health/topics/depression/index.shtml. Retrieved 15 October 2012.
8. O'Donnel JM. Shelton RC. Hypnotics and sedatives. In: Brunton LL, Chabner BA, Knollmann BC, eds. Goodman andGilman's: The pharmacological basis of therapeutics. 12th edition. New York. McGraw-Hill;2011:607-629.
9. American Psychiatric Association. Practice Guidelines for the Treatment of Psychiatric Disorders: Compendium 2004. Arlington, Va: American Psychiatric Association. 2004
10. Shader RI, Greenblatt DJ. Approaches to the treatment of anxiety states. In: Shader RI, ed. Manual of Psychiatric Therapeutics Third ed. Philadelphia, Pa: Lippincott Williams and Wilkins. 2003:184-209.
11. Sheeran T, Zimmerman M. Social phobia: still a neglected anxiety disorder? J Nerv Ment Dis. 2002;190:786-8.
12. Nutt DJ. Overview of diagnosis and drug treatments of anxiety disorders. CNS Spectr. 2005;10:49-56.
13. Susman J, Klee B. The role of high-potency benzodiazepines in the treatment of panic disorder. Prim Care Companion J Clin Psychiatry. 2005;7:5-11.
14. Berk M. Selective serotonin reuptake inhibitors in mixed anxiety-depression. Int Clin Psycho Pharmacol. 2000;15(2):S41-S45.
15. Williams JB, Kobak KA. Development and reliability of a structured interview guide for the Montgomery-Åsberg Depression Rating Scale (SIGMA). Brit J Psychiatry. 2008 Jan;192(1):52-8.
16. Stein DJ. Comorbidity in generalized anxiety disorder: impact and implications. J Clin Psychiatry. 2001;62(Suppl 11):29-34.
17. Attending to anxiety disorders in primary care. Stein MB J Clin Psychiatry. 2003;64 Suppl 15:35-9.
18. Gorwood P. Generalized anxiety disorder and major depressive disorder comorbidity: an example of genetic pleiotropy?. European Psychiatry. 2004 Jan 1;19(1):27-33.
19. Weisberg RB, Dyck I, Culpepper L, Keller MB. Psychiatric treatment in primary care patients with anxiety disorders: a comparison of care received from primary care providers and psychiatrists. American J Psychiatry. 2007 Feb;164(2):276-82.
20. Smith WT, Londborg PD, Glaudin V, Painter JR. Short-term augmentation of fluoxetine with clonazepam in the treatment of depression: a double-blind study. Am J Psy. 1998;155(10):1339-45.
21. Goddard AW, Brouette T, Almai A, Jetty P, Woods SW, Charney D. Early coadministration of clonazepam with sertraline for panic disorder. Archives General Psychiatry. 2001;58(7):681-6.
22. Pollack MH, Simon NM, Worthington JJ, Doyle AL, Peters P, Toshkov F, et al. Combined paroxetine and clonazepam treatment strategies compared to paroxetine monotherapy for panic disorder. J Psychopharmacol. 2003 Sep;17(3):276-82.
23. Seedat S, Stein MB. Double-blind, placebo-controlled assessment of combined clonazepam with paroxetine compared with paroxetine monotherapy for generalized social anxiety disorder. J Clin Psychiatry. 2004;65:244-8.
24. Birkenhager TK, Moleman P, Nolen WA. Benzodiazepines for depression? a review of the literature. Int Clin Psycho Pharmacol. 1995;10:181-95.
25. Mirowsky J. Age and the gender gap in depression. J Health and Social Behavior. 1996 Dec 1:362-80.

26. C Pollack MH, Simon NM, Worthington JJ, Doyle AL, Peters P, Toshkov F, et al. Combined paroxetine and clonazepam treatment strategies compared to paroxetine monotherapy for panic disorder. J Psychopharmacol. 2003;17(3):276-82.
27. 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;61:73-9.
28. Furukawa TA, Streiner DL, Young LT. Antidepressant and benzodiazepine for major depression. Cochrane Database Syst Rev. 2002;1:CD00026.
29. Murphy JM. Diagnosic comorbidity and symptom cooccurence: the Stirling County Study. In: Maser JD, Cloninger CR editor(s). Comorbidity of Mood and Anxiety Disorders. Washington DC: American Psychiatric Press;1990:153-76.
30. Bouhassira M, Allicar MP, Blachier C, Nouveau A, Rouillon F. Which patients receive antidepressants? A 'real world' telephone study. J Affective Disorders. 1998;49(1):19-26.
31. Rickels K, Schweizer E, Case WG, Greenblatt DJ. Long term therapeutic use of benzodiazepines. I. Effects of abrupt discontinuation. Archives of General Psychiatry. 1990;47(10):899-907.
32. Spiegel DA. Psychological strategies for discontinuing benzodiazepine treatment. J Clin Psycho pharrnacol. 1999;19(6suppl2):17S-22S.
33. Schweizer E, Rickels K, Case WG, Greenblatt DJ. Long-term therapeutic use of benzodiazepines. II. Effects of gradual taper. Arch Gen Psychiatry. 1990;47:908-16.

Cite this article as: Dar SA, Bhat BA, Jan MM. Addition of benzodiazepines to selective serotonin reuptake inhibitors to optimize treatment of depression: a hospital based study. Int J Res Med Sci 2018;6:2081-5.