A PROSPECTIVE COMPARATIVE STUDY ON TOLERABILITY AND SAFETY OF AMITRYPTILINE AND FLUOXETINE IN PATIENTS WITH DEPRESSION

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ABSTRACT
Depression is a disorder of public health importance, in terms of its prevalence, morbidity, mortality and economic burden. Amitriptyline is a tricyclic antidepressant group, its use has been declining due to their unfavorable side effect profile. Selective serotonin reuptake inhibitors (SSRI) were introduced with the aim of reducing the side effects and increasing the tolerability and they were believed to overcome the difficulties of TCA. We planned to study the tolerability and side effect profile of tricyclic antidepressants and selective serotonin reuptake inhibitors in patients with depression.

METHODOLOGY: Eighty clinically diagnosed patients of depression, after obtaining institutional ethical clearance and informed written consent from them, were divided into two groups and they received amitriptyline and fluoxetine for a period of 8 weeks. Clinical assessment of Safety parameters of both antidepressants were done at the beginning of the study and on 2nd, 4th, 6th, 8th weeks. The safety profile was assessed by comparing the adverse effects in the patients of both groups with a standard adverse effect checklist and based on previous literature for the study. The tolerability of the two antidepressants was assessed by calculating the number of patients presenting with adverse effects during the follow-ups in both the groups.

RESULTS: Fluoxetine showed better tolerability than Amitriptyline in patients with depression. Amitriptyline caused more adverse effects than fluoxetine. Anticholinergic side effects were seen more in the amitriptyline group than the fluoxetine group.
KEYWORDS: Antidepressants, Fluoxetine, Amitriptyline, Safety, Tolerability.

INTRODUCTION
Depression is a common mental problem faced by many persons and it presents with depressed mood, lack of interest, loss of pleasure, feeling guilt, low self-worth, sleep disturbances, loss of appetite, low energy and poor concentration. Depression is a disorder of public health importance, in terms of its prevalence, morbidity, mortality and economic burden. The prevalence of depression is more in women than men. According to the report on the global burden of disease the estimated point prevalence of depressive episodes among men was 1.9% and in women 3.2%.[1] It is possible to treat the depressed patient in primary care level and the trend has turned from custodial care towards restoring the individual patient to his place in community.[2] There are many classes of antidepressants and the list is growing with the advent of many newer anti-depressants, tricyclic anti-depressants (TCA) were initially used to treat depression. Amitriptyline is an effective anti-depressant belonging to a tricyclic antidepressant group. Though it is highly efficacious its use has been declining due to their unfavorable side effect profile. The search for newer antidepressants began with the aim of identifying a drug with less side effects and better tolerability and efficacy. Selective serotonin reuptake inhibitors (SSRI) were introduced with the aim of reducing the side effects and increasing tolerability and they were believed to overcome the difficulties of TCA. SSRI is the currently preferred first line anti-depressant of choice in unipolar depression.[3] Fluoxetine is a selective serotonin reuptake inhibitor, which is introduced first in this class. It is a long acting drug and it is approved for use in children seven years and above and elders for depression.[4] We planned to study the side effect profile of tricyclic antidepressants and selective serotonin reuptake inhibitors in patients with depression in a psychiatric outpatient department in a government tertiary care hospital using amitriptyline and fluoxetine as the candidate drug.

MATERIALS AND METHODS
Study was carried out in the outpatient department of psychiatry, Government Rajaji Hospital, Madurai, after obtaining clearance from Institutional ethical committee, Government Rajaji Hospital, Madurai. The study was designed as an Single center, open labeled, Prospective, observational study with sample size of eighty patients divided into two treatment arms with forty patients in each arm. Written informed consent was obtained from all the patients. Newly diagnosed patients suffering from depression (moderate to severe)
according to ICD 10 criteria attending psychiatric outpatient department were selected for the study with the age group of 19 to 60 years of both sex and those willing to participate in the study. Subjects were explained about the proposed study, the need for follow up. Only those subjects who accepted to adhere to this guideline were considered for the study

Patients less than 19 years, more than 60 years, those not willing to participate in the study were excluded. pregnant and breastfeeding mothers were excluded. Patients with cardiac disease, diabetes mellitus, hypothyroidism, and obesity were excluded. Patients with hepatic disease were excluded from the study. Those with acute or chronic renal problems were excluded. Patient with tuberculosis, HIV/AIDS, leprosy were excluded from the study. Patients with any other comorbid conditions were excluded. Patients were permitted to discontinue at any time during the study, and when the patient was found to develop another illness or worsening of existing illness or requiring additional drugs, they were withdrawn from the study.

Eighty Cases were selected over a period of one year. Counseling was given to them on proposed study for this purpose. Patients were informed verbally and in writing by the investigator about the nature, significance, Implications and risks of the study prior to enrollment. Informed consent was obtained from all the patients. They were divided into two groups and group I was given amitriptyline and group II was given fluoxetine. Socio-demographic data was collected from the participants. The strips of tablets were cut into single units and the required number of tablets for 15 days were placed in a cover and given to patients and they were asked to bring empty blister packs for pill counting. They were advised not to take any other medications without the knowledge of investigator. Study participants were advised to return the used blister packs at the next visit in order to maintain accountability of study medication. Clinical signs of intoxication were explained and instructions were given to avoid overdose.

Patients were given treatment for a period of 8 weeks and they were followed were once in two weeks. Complete blood count, Liver function test, renal function test, Thyroid profile, blood glucose and serum cholesterol were estimated at baseline and at the end of study for all the patients. Clinical assessment of Safety parameters of both antidepressants were done at the beginning of the study and on 2nd, 4th, 6th, 8th weeks. The safety profile was assessed by comparing the adverse effects in the patients of both groups with a standard adverse effect checklist and based on previous literature for the study. The tolerability of the two
antidepressants was assessed by calculating the number of patients presenting with adverse effects during the follow-ups in both the groups.

Data were entered in Microsoft excel sheet and analyzed using descriptive statistics and student’s t test for normally distributed data.

RESULTS
All the patients completed the 8 weeks trial and there was no drop out in the study, all the 80 patients were analyzed for tolerability to antidepressants and side effect. Among eighty patients analyzed 46 % were males and rest were females (54%) Among eighty patients included the age related distribution were 37% were in the age group of 20-29 years, 27% in 30-39 years, 22% belonged to 40-49 years while 14 % belonged to 50-59 years. The majority of patient belonged to 20-39 years of age (64%).

![Figure-1: Tolerability of Antidepressants](image)

The tolerability of the two antidepressants was evaluated by counting the number of adverse effects reported by the patients as compared with the standard adverse drug check list prepared for the study. Accordingly the tolerability was graded as excellent if patient had no adverse effects during the study period, good if one or two adverse effects, moderate if patient had three to four adverse effects and they were graded as bad if they had five or more adverse effects during the study period In amitriptyline group, no patient showed excellent tolerability, 24(60%) patients had good tolerability, 15(37%) patients had moderate tolerability and one (2%) patient had bad tolerability. In fluoxetine group, 8(20%) patients had excellent tolerability, 23(57%) patients had good tolerability while 9(22%) patients had moderate tolerability and no patient showed bad tolerability.
DISCUSSION

Mood disorders are a group of disorders characterized by altered regulation of mood, behavior and affect. Introduction of new class of antidepressants has significantly changed the management of depression, early identification and treatment at the grass root level that is the primary care level may be beneficial to the patient in reducing the suffering. The pharmacological management of depression has seen many advances with the advent of newer drugs, the therapy of depression has changed from tertiary care to primary care The continuous effort of many researchers globally has given us many pharmacological tools to treat the depression. Drugs with better efficacy tolerability and lower side effects were the preferred when compared to older antidepressants which have many adverse effects.
Amitriptyline is a tricyclic antidepressant, its efficacy is well established in severe depression but its usages have declined because of adverse effects and poor tolerability. Fluoxetine being an SSRI claimed to be equally effective as TCA in treating depression with better tolerability and with less side effects. Data on the response to drug therapy for antidepressants among the South Indian population is unavailable in detail. A metanalysis by Siddarth Sarkar and Sandeep Grover has reviewed the efficacy of treatment of depression in Indian context and they have found there were some data from India with respect to the efficacy of antidepressants they have found most of the trials have been shorter duration and has been inadequately powered. The available data shows the superiority of antidepressants over placebo.\cite{5}

In a total of eighty patients who participated in the study, 65% of patients were in the age group of 20-40 years. Epidemiological studies have clearly shown a higher prevalence of all mood disorder under the age group of 40 years.\cite{6} 65% patient were in the most productive phase of life that is 20-39 years and the elderly patients were 16% that is patients more than 50 years of age. A systematic review by Machine G Cole and Nandhini dendukuri has included 20 studies assessing the risk factors for depression among elderly community subjects and found sleep disturbances, disability, prior depression and female gender to be important risk factors for depression among elderly community subjects.\cite{7} Out of eighty patients who participated in the study, 46% were males and 54% were females. We have found that depression is more female than male. Study by MM Welshman and Molfson has confirmed the prevalence of depression is approximately twice more common in women than man by studying the epidemiological data on depression worldwide.\cite{8}

Comparing the tolerability of two antidepressants showed that 20% of patients in the fluoxetine group had excellent tolerability while in the amitriptyline group no patients had excellent tolerability. Similarly 57 % and 22 % patients in amitriptyline and fluoxetine group respectively showed good tolerability while 60% and 37 % in both groups had moderate tolerability and 3% in amitriptyline had bad tolerability and none in the fluoxetine group had bad tolerability. When both group were compared, fluoxetine group showed better tolerability and which is statistically significant (p < 0.05) compared to amitriptyline group. A systematic review by Carrado Barburi and Mathew Hotopf has reviewed the tolerability of amitriptyline in the management of depression and they have included 186 RCT in their review and they have found amitriptyline is less tolerated than SSRI.\cite{9}
The incidence of anticholinergic side effects was more in the amitriptyline group when compared to the fluoxetine group. The troublesome anticholinergic side effects were more common in the amitriptyline group, due to the side effects the tolerability of the amitriptyline is low even though it is equally effective as fluoxetine in management of depression. The anticholinergic side effects may be dangerous in the elderly population so that use of amitriptyline in elderly patients needs caution. A study by Jacob Mintzer et al has studied anticholinergic side effects of drugs in elderly people and they have found the use of antidepressants in elderly people requires particular care, imipramine and amitriptyline produce postural hypotension, sedation, urinary retention, constipation, confusion which are troublesome. The selective serotonin reuptake inhibitor such as fluoxetine is safe in this aspect and they are recommended in elderly because of their freedom from anticholinergic side effects.\textsuperscript{[10]}

The fluoxetine group had side effects related to gastrointestinal system nausea 22%, diarrhea in 7% of patients, anorexia in 17% of patient’s, central nervous system related side effects were sedation 17%, anxiety 20%, tremor in 12% of patients insomnia in 27% of patients, dry mouth was reported by 7% of patients. Fluoxetine being an SSRI is devoid of anticholinergic side effects, the side effect of fluoxetine is more gastrointestinal related and which is tolerated by the patients. Hence fluoxetine is having better tolerability than amitryptine, and the side effects were very minimal. A Metanalysis by Barambilla etal has found significant less percentage of patients treated with fluoxetine experienced side effects when compared to TCA. fluoxetine was better tolerated in comparison with TCA and regarding to individual side effects insomnia, agitation, anxiety and gastrointestinal side effects like nausea, vomiting, anorexia were significantly more frequent in fluoxetine treated patients.\textsuperscript{[11]} The observed biochemical parameters in our study were normal for all the study participants after completing the study, there were no electrocardiographic abnormalities among the study participants after completing the study.

CONCLUSION
We conclude that the tolerability of fluoxetine is better than amitriptyline and it is statistically significant. Anticholinergic side effects were seen more in the amitriptyline group than the fluoxetine group. Amitriptyline is a tricyclic antidepressant, its efficacy is well established in severe depression but its usages have declined because of adverse effects and poor tolerability. Fluoxetine being an SSRI claimed to be equally effective as TCA in treating
depression with better tolerability and with less side effects. Small sample size, lesser duration of study and open labeled non blinded techniques are the limitations of our study hence we recommend further study with a large sample size and longer duration to generalize the results of the study. Early identification and treatment of depression at the primary care level by the primary care physicians may bring a change in the medical and social problems created by depression.

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