e-ISSN: 0975-5160, p-ISSN: 2820-2651

Available online on www.ijtpr.com

International Journal of Toxicological and Pharmacological Research 2022; 12(2); 47-53
Original Research Article

Effect Of Amitriptyline and Fluoxetine in Patients Presenting with Mixed Anxiety and Depression: Comparative Study

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Received: 04-09-2021 / Revised: 28-10-2021 / Accepted: 10-01-2022
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Conflict of interest: Nil

Abstract

Aim: Comparative study of efficacy of amitriptyline and fluoxetine in patients presenting with mixed anxiety and depression

Materials and Methods: This comparative study was carried out in the Department of Psychiatry, Jawaharlal Nehru Medical College, Aligarh Muslim University, Aligarh, UP, India, for 15 months. Fifty-eight patients (25 male and 25 female) from 3 sites were enrolled in the study. Ages ranged from 20 to 60 (mean = 41.11 k 9.11) years.

Results: 50 patients were taken in the study and were divided into two groups with each group holding 25 patients. Two drugs namely fluoxetine and amitriptyline taken in study to determine their effects on two groups (25 on fluoxetine and 25 on amitriptyline) completed. As noted, fluoxetine was given at a fixed dose of 20 mg/day for the duration of the study. The dose of amitriptyline was gradually increased to 150 mg over the first 2 weeks. By week 6, 12 (55%) of the patients on amitriptyline were taking 200 mg/day and the remainder 150 mg/day. Compliance as reported to the treating physician varied from 85-100% of patients at any one visit. Approximately half of the patients in each treatment group (fluoxetine 16/25, amitriptyline 17/25) were on concomitant non-psychotropic medications at the start of the trial (p>O. 1, chi square test). Both treatments produced a statistically significant reduction in HDRS score from baseline as assessed by the repeated measures analysis of variance (p<O.O001).

Conclusion: We concluded that the fluoxetine 20 mg/day is effective in the acute treatment of patients with moderately severe depression. It appears to be well tolerated, with a different side-effect profile from that of amitriptyline.

Keywords: Fluoxetine, Amitriptyline, HDRS.

Introduction

Childhood and adolescence are risk periods for the development of psychiatric disorders, and major depressive disorder is a leading contributor to burden of disease in young people aged 10–24 years [1]. In England in 2017, major depressive disorder in children and adolescents was common, with an estimated point prevalence of about 0·3% in children (5–10 years), 2·7% in younger adolescents (11–16 years), and 4·8% in older adolescents (17–19 years) [2]. The course of this disorder is often characterized by heterogeneous symptoms (eg. irritability, aggressive behaviors, and school refusal), protracted episodes, frequent recurrence, and co morbid psychiatric disorders [3]. Young patients with depression have more serious impairments in social and educational functioning and have an increased risk of smoking, substance misuse, obesity, and suicide compared with adults with depression. Moreover, depression is the second or third leading cause of death in adolescence [4].

In the past two decades, pharmacological and psychological interventions have been widely used in the treatment of depressive disorder in children and adolescents worldwide [5]. In 2005–12, the prevalence of antidepressant uses in children and adolescents increased from 1·3% to 1·6% in the USA and from 0·7% to 1·1% in the UK [5]. As the first-line treatment, psychotherapies, especially cognitive-behavioural therapy (CBT) and interpersonal psychotherapy, appeared to be more effective compared with psychological controls in previous meta-analyses [7,8]. The mean effects (standardised mean difference [SMD] −0.29) after treatment were more modest than those found for treatment of other youth problems, including anxiety (SMD −0.61), attention deficit hyperactivity disorder (SMD −0.34), and conduct-related problems and disorders (SMD −0.46) [9]. Previous meta-analyses [10,11] have shown that antidepressants, except for fluoxetine, do not offer a clear advantage over pill placebo for many individuals, and some antidepressants might increase risk of suicidality. The mean effects of antidepressants for major depressive disorder compared with pill placebo (Hedges g 0.21 for selective serotonin reuptake inhibitor [SSRI] and 0·16 for serotonin-norepinephrine reuptake inhibitor [SNRI]) have been more modest than those found for treatment of other youth problems, including anxiety disorder (Hedges g 0·71 for SSRI and 0·41 for SNRI) and obsessive-compulsive disorder (Hedges g 0.39 for SSRI) [12].

Whether the combination of antidepressant and psychological interventions is more beneficial than antidepressants alone remain unclear [13]. The aim of this study was to synthesise all the available evidence on commonly used antidepressants, psychotherapies, and their combinations for the acute treatment of depressive disorder in children and adolescents.

Material and methods:

This comparative study was carried out in the Department of Psychiatry, Jawaharlal Nehru Medical College, Aligarh Muslim University, Aligarh, UP, India, for 15 months

Methodology:

Fifty-eight patients (25 male and 25 female) from 3 sites were enrolled in the study. Ages ranged from 20 to 60 (mean=41.11 k 9.11) years. All 50 patients met DSM-111-R criteria for major depressive disorder, with the additional requirements of an episode duration of at least one month, and the illness being of at least moderate severity (initial score of >I7 on 17-item Hamilton Rating Scale for Depression) [14]. Other provisional

patients were excluded from the study if they met any of the following DSM-111-R diagnoses: organic mental disorder, substance use disorder, schizophrenia or schizoaffective disorder, paranoid or other psychotic disorder, bipolar disorder. Also excluded were depressed patients with significant physical illness, or with a history of seizures, drug allergy, glaucoma or urinary retention; those requiring antihypertensive or other psychotropic medication including lithium; as well as pregnant or lactating women. Patients recruited to the study attended for an initial screening visit to determine their suitability. A detailed psychiatric assessment, as well as physical examination, biochemical and haematological screen and ECG, were carried out at this visit. Suitable patients were then entered into the study and treated on a single-blind basis with placebo for one week (two weeks if previously taking a MAOI). Patients in whom the Hamilton Depression Score fell to below 2/3 of the initial value after one week of placebo did not progress to the double-blind phase of treatment. Patients were allocated randomly to treatment with either amitriptyline or fluoxetine. Medication was given in matching capsules (i.e., amitriptyline 50 mg capsules and matching placebo, or fluoxetine 20 mg capsules and matching placebo). The dosage of amitriptyline was increased according to patient tolerance to reach 150 mg/day by the end of week 2, when dosage could be further adjusted according to clinical response to a maximum of 200 mg/day. The dose of fluoxetine was 20 mg/day for 4 weeks. Fluoxetine was administered in the morning (and placebo at night), and amitriptyline in the evening (with morning placebo). Patients who showed a significant clinical response to fluoxetine after 6 weeks were able to continue on the medication. The only medication permitted for night sedation was either chloral hydrate or temazepam. Patients were seen weekly during the 4-week double-blind phase of treatment. Clinical assessment was made at interview and by use of the Hamilton and Carroll [15]. depression rating scales with systematic enquiry about possible side-effects. Blood was drawn for plasma drug screen at the initial visit and visits at the end of 2 and 4 weeks of treatment. Biochemical and haematological screen, as well as an ECG, were repeated after 4 weeks of treatment.

Results:

50 patients were taken in the study and were divided into two groups with each group holding 25 patients. Two drugs namely fluoxetine and amitriptyline taken in study to determine their effects on two groups (25 on fluoxetine and 25 on amitriptyline) completed. As noted, fluoxetine was given at a fixed dose of 20 mg/day for the duration of the study. The dose of amitriptyline was gradually increased to 150 mg over the first 2 weeks. By week 6, 12 (55%) of the patients on amitriptyline were taking 200 mg/day and the remainder 150 mg/day. Compliance as reported to the treating physician varied from 85-100% of patients at any one visit. Approximately half of the patients in each treatment group (fluoxetine 16/25, amitriptyline 17/25) were on concomitant non-psychotropic medications at the start of the trial (p>O. 1, chi square test).

Table 1: Hamilton total score

Treatment			Week			
	A	B	1	2	3	4
FLUOXETINE						
MEAN	26.2	26.4	22.5	21.9	18.7	15.8
SD	7.0	6.2	9.0	8.4	7.1	8.2
AMITRIPTYLINE						
MEAN	26.0	25.7	21.4	20.5	18.6	17.7
SD	6.4	5.7	6.7	7.7	7.8	8.9

Visit A = screening visit From A to B (baseline) placebo prescribed From B to week 4 active drug prescribed.

Table 2: Carroll total score

Treatment			Week			
	A	B	1	2	3	4
FLUOXETINE						
MEAN	32	31	26	26	22	20
SD	10	10	12	12	12	12
AMITRIPTYLINE						
MEAN	31	29	25	23	23	22
SD	8	9	11	11	10	12

Visit A = screening visit From A to B (baseline) placebo prescribed From B to week 4 active drug prescribed Data from two subjects in both treatment groups was not recorded at pre-treatment visit (A)

Table 3: The most common adverse events

Adverse events	Fluoxetine	Amitriptyline	
Blurred vision	10	14	NS
Constipation	5	15	p<0.005
Dry mouth	10	22	p<0.005
Headache	14	12	NS
Insomnia	9	6	NS
Jerky limbs	7	6	NS
Nausea	10	8	NS
No libido	8	4	NS
Sedation	7	18	p<0.005

*Results of chi square analysis with Yates' correction applied NS = not significant

Scores on the Hamilton Depression Rating Scale (HDRS) decreased over time in the six-week study for both treatment groups (Table 1). Both treatments produced a statistically significant reduction in HDRS score from baseline as assessed by the repeated measures analysis of variance (p<O.O001). There were no statistically significant differences between drugs at any visit (p>O. I, MANOVA). Comparing mean individual HDRS item ratings revealed few statistically significant differences between groups.

Somatic anxiety showed greater improvement in fluoxetine-treated patients (~4.003 MANOVA) while middle insomnia (pO. 1 MANOVA) between the two treatment groups at any visit.

Side-effects were recorded if reported spontaneously by the patient. The presence of side-effects tended to be greater in the amitriptyline group than in the fluoxetine group at each visit. During the double-blind period, 45%, 62%, 54%, 70%, 46% and 35% of patients receiving fluoxetine reported at least one side effect at weeks 1, 2, 3, 4, respectively. In contrast, reporting at the same visits in the amitriptyline group was 86% 89%, 84%, 75%, 85% and 83%. There was a statistically significantly greater occurrence of constipation, dry mouth and sedation in the amitriptyline treated patients (Table 3). The most common adverse events are shown in Table 3. No clinically significant changes in haematology, biochemistry or ECG results were found in association with either drug.

The mean HDRS item 3 score for suicidal ideation in both the amitriptyline and fluoxetine-treated patients decreased significantly over time (p>0.0005 MANOVA). There was no evidence from chi square analysis of any selective increase in suicidal ideation for fluoxetine treated patients.

In the fluoxetine-treated patients suicide scores increased for two patients. One patient who started at zero at baseline increased to 2 at weeks 4 and 5 and was subsequently withdrawn from the study. For the other patient, the baseline rating of 2 increased to 3 at week and decreased to 2 at week 2 of treatment at which time the patient was withdrawn from the study. Neither patient was withdrawn because of the change in suicidal ideation. For the amitriptyline group, suicide scores also increased for two patients. One patient whose score was 1 at baseline, increased to 3 at week 3 but subsequently decreased. The second patient whose baseline score of 2 increased to 3 at week 4 was then withdrawn from the study. One patient had a baseline score of 3, which initially decreased but again increased to 3 at weeks 5 and 6. Discussion The main aim of this study was to compare the antidepressant efficacy of fluoxetine (at a fixed dose of 20 mg/day) to amitriptyline. Previous studies using 20 mg/day of fluoxetine have used low dose tricyclic as the comparator [16,17].

We administered amitriptyline in doses commonly used for the treatment of moderately severe depression (150-200 mg/day). Patients in both treatment groups were moderately severely depressed (mean HDRS score 26.4,25.7) on entry to the study. Both groups showed clinically significant improvement over the 6 weeks of the study, with no statistically significant difference demonstrated between groups. The latter is to be expected; a 10% difference in response would require approximately 200 patients in each treatment group [18].

While some difference in rate of improvement of individual depressive symptoms was demonstrated, the overall rate of improvement was equal in both groups. The greater improvement in late and middle insomnia in amitriptyline-treated patients may be attributed to the sedative effects of that tricyclic drug. Comparative statistical analysis showed that the mean score for suicidal ideation decreased during treatment for both drugs significantly. Contrary to previous reports [19,20] no exacerbation of suicidal ideation was seen in any of the fluoxetine-treated patients using the definition of Beasley et a1 [21] (i.e., no patient had an increase in item 3 score of Hamilton Depression Rating Scale from 0 or 1 at baseline to 3 or 4 at any time during the

6 weeks treatment). Overall, fluoxetine was well tolerated by patients. Fewer adverse effects were reported by patients taking fluoxetine than by those taking amitriptyline. The frequency of reporting anticholinergic effects was markedly more frequent in the group treated with amitriptyline. Side-effects commonly attributed to fluoxetine [22] (nausea, tremor, headache) were found with similar frequency in both groups. Poor libido and skin rash (not necessitating withdrawal from the study) were reported more by the fluoxetine-treated patients.

Conclusion:

We concluded that the fluoxetine 20 mg/day is effective in the acute treatment of patients with moderately severe depression. It appears to be well tolerated, with a different side-effect profile from that of amitriptyline.

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