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WHICH ANTIDEPRESSANTS ARE BEST TOLERATED IN PRIMARY CARE? A PILOT RANDOMIZED TRIAL FROM GOA

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ABSTRACT

Even though cultural, biological and health service factors influence the tolerance and acceptability of psychotropic drugs in different settings, there is a lack of data on the use of antidepressants in primary care settings from India. The aim of this study was to examine the tolerance of 3 models of antidepressants treatments (fluoxetine 20 mg; imipramine 75 mg; imipramine 150 mg) for commoh mental disorders in attenders at a primary care clinic in Goa. The study design was a randomized trial. A total of 61 adult subjects with a common mental disorder were recruited and randomized to one of the 3 groups. Subjects were reviewed at 2 and 6 weeks. The main outcome measures were discontinuation rates. The key findings are that while discontinuation rates are higher in subjects on imipramine 150 mg as compared to the other groups, the majority of subjects in all groups discontinued their medication. The commonest reasons for discontinuation are anticholingeric and hypotensive side effects.

Key words : Antidepressant, randomized trial, discontinuation rates

Common Mental Disorders (CMD) are disorders characterised by the presentation of nonspecific, multiple somatic symptoms, sleep disturbances and psychological symptoms of anxiety and depression. CMD are amongst the most frequent and most disabling of all disorders encountered in primary care (Ormel et al.,1994). Psychiatric morbidity can be detected in up to half of adult PHC attenders in India (Shamasundar et al.,1986; Sen,1987). CMD accounts for most of this morbidity, up to two-thirds of which is unrecognized and either untreated to treated with inappropriate medication. This sub-optimal management leads to persisting symptoms, excess health service use and loss working ability (Patel et al.,1998a; 1998c).

The aim of the trial described in this paper was to compare the tolerance and side-effects profile of patients attending primary health clinics [PHC] with a CMD, comparing 3 groups: imipramine 150 mg which was the dose recommended by psychiatric textbooks; imipramine 75 mg which is the maximum dose generally prescribed by private practitioners; and fluoxetine 20 mg which is rarely prescribed in primary care due to the perceived higher costs. The specific objectives of the trial were to address the following questions :

1) Which group of anti-depressant therapy is more acceptable in terms of side effects profile and patient compliance as estimated by side effect checklists and discontinuation rates ?

2) This study is, to the best our knowledge, the first double blind randomized trial of antidepressants in primary care in India. Thus, the study was designed as a pilot trial with the aim of identifying the antidepressant of choice for a definitive trial in general health care and to determine the feasibility of large trials in this setting.

MATERIAL AND METHOD

Site : Peri urban PHC in the state of Goa on the west coast of India.

Population : Outpatient attenders.

Sample Selection : This is outlined in figure 1.

Recruitment Procedure : A standard two stage process of selecting subjects with CMD was employed. The 5 item Konkani GHQ was used as a screening questionnaire and the Revised Clinical Interview Schedule as a second stage diagnostic interview for CMD. The CISR is a structured interview for the measurement of CMD in community and primary care settings (Lewis et al.,1992). Details of the translation and use of the Konkani versions of the CISR and the validation of the GHQ-5 in an earlier study in primary care are published elsewhere (Patel et al.,1998b).

Written Informed Consent : Written informed consent provided information advising the subject about the blind nature of the treatment, potential side-effects and the freedom to drop-out if they wished before the completion of the trial.

Sample Size & Randomization : A sample of 61 out patient attenders were recruited on the basis of the steps outlined in figure 1. Power calculations were not undertaken because of the unknown level of expected drop-out rates for the different drug groups and due to the pilot nature of the trial. Subjects were then randomized to any of 3 treatment groups based on an allocation schedule generated by a simple randomization table.

Randomization Groups :

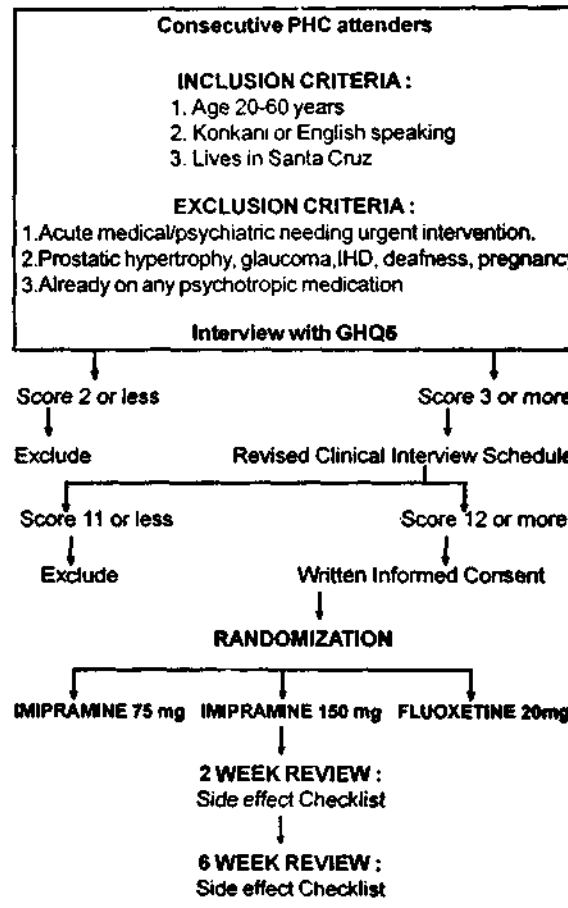
1. Imipramine 75 mg : this group received 50 mg for 1 week which was increased to 75 mg afterwards. All medication was taken at bedtime.
2. Imipramine 150 mg : this group received 50 mg for 1 week, 75 mg in the second week and 150 mg thereafter. All medication was taken at bedtime.
3. Fluoxetine : this group received 20 mg in the morning daily throughout.

Blinding : All the patients were ultimately receiving the drugs in a capsule form in sealed packets at recruitment (2 week supply) and at two week follow up (4 week supply). The allocation schedule regarding the type of medication and randomization of patients in the trial which were held by the first author were broken only when the trial was completed. The interviews were carried out by two investigators who were blind as to what treatment the patients were receiving.

Outcome Assessments : Patients were assessed at 2 weeks and 6 weeks after recruitment. Subjects who failed to take 75% of the medication in the period prior to review were considered to have been noncompliant (discontinuation rate). Subjects who discontinued were asked open questions about the reasons for noncomplying.

Analysis : Drop-out rates were compared between the 3 groups using odds ratios.

FIGURE 1
FLOW CHART OF ANTIDEPRESSANT TRIAL



RESULT

The Sample : A total of 61 subjects were recruited. The mean age was 46.5 years (sd 10.75 range 25-60 years). Females constituted about

97% of the total while only 3% were males. Majority of the patients (77%) had not completed school, while 23% had finished their SSC. 59% of the patients were married while 39% patients were widowed. 80% of the patients were unemployed while only 13% were engaged in skilled labor. Catholics constituted 59% while 38% were Hindus. The mean CISR scores was 25 (sd 8; Range : 12-43). Of the 61 subjects, 58 were traced for interview at 2 and 6 weeks providing a follow-up rate of over 95%.

Adequacy of Randomization : 21 subjects received fluoxetine, 20 received imipramine 75 mg and 20 received imipramine 150 mg. All three treatment groups were well matched after randomization with respect to age (p=0.52); CISR scores at recruitment (p=0.69) and gender.

Diagnostic Categories : The commonest ICD-10 diagnoses were those of depressive disorder and mixed anxiety depressive disorder (table 1).

TABLE 1
ICD-10 DIAGNOSTIC CATEGORIES OF SUBJECTS IN THE TRIAL

ICD-10	No.	%
Mild depressive episode	7	15
Moderate depressice episode	16	33
Severe depressive episode without psychotic symtoms	11	23
Panic disorder	2	4
Mixed Anxiety and Depressive disorder	23	38
Neurasthenia	2	4

Discontinuation Rates and Side-effects : Discontinuation rates for the 3 groups at 2 and 6 weeks follow-up are presented in table 2. The main finding was that the highest proportion of treatment completers was in the fluoxetine group. However, even in this group, the majority of subjects did not complete the medication regime. There was no significant difference in discontinuation rates between fluoxetine and imipramine 75 mg. However, subjects in the imipramine 150 mg group were more likely to discontinue when compared to subjects in the other two groups combined. Thus, at 2 weeks, the odds for a subject on imipramine 150 mg to discontinue was 2.8 (95% CI 0.7-11.1) and at 6 weeks it was 2.3 (95% CI 0.5-12.2). Out of the 40 patients from the original sample who did not complete the trial 33 patients (82.5%) discontinued due to side effects of medication. The commonest side effects seen at 2 weeks were palpitations, giddiness, blurring of vision, dryness of mouth, drowsiness, restlessness, confusion and headache. While anticholinergic side effects and giddiness (possibly related to postural hypotension) were common in the imipramine groups, headaches and restlessness were common in the fluoxetine group.

Predictors of Outcome Based On Recruitment Variables : The greater the age of the person, more were the odds of completing the trial (OR=1.1, 95% CI=1-1.19, p=0.015). Religion was the other factor with the odds greater for Catholics completing the trial (OR=3.6, 95% CI=0.9-14.7, p=0.06). Recruitment CISR score, occupation, marital status and qualification were not related to drop-out rates.

TABLE 2
OUTCOME OF DISCONTINUATION AND COMPLETION RATES

Drug Type		FT	DO2	DO6	Unknown/Lost	Total
Fluoxetine	N	7	8	4	2	21
	%	33.3%	38.1%	19.05%	9.5%	
Imipramine	N	5	11	4	0	20
75 mg	%	25%	55%	20%		
Imipramine	N	3	14	2	1	20
150 mg	%	15%	70%	10%	5%	
Total	N	15	33	10	3	61
	%	29.5%	54.10%	16.3%	4.9%	

FT=Completed trial, i.e. took>75% medication for full duration of trial
DO2= Discontinued between recruitment and followup at 2 weeks
DO6=Discontinued between followup at 2 weeks and followup at 6 weeks

DISCUSSION

There is a growing literature on the effectiveness of antidepressant and psychological interventions for CMD from developed societies (Paykel & Priest,1992). Given the varying nature of the health systems and cultures in low-income countries, it is necessary to evaluate the effectiveness of treatments for CMD in these settings. An example of this variability is the cost of drugs in different health systems. Thus, SSRIs cost substantially more than older tricyclics in developed countries leading to a recommendation to use the latter inspite of the higher risk of side-effects and drop-outs (Hotopf et al.,1996 & 1997). However, due to the deregulation of the pharmaceutical industry in India, SSRIs such as fluoxetine in therapeutic doses have a comparable cost to older tricyclics and are cheaper than the newer tricyclics (Patel, 1996). Similarly, anecdotal and clinical evidence from India and other low-income settings suggest the therapeutically effective dose of tricyclic anti-depressants is lower than that recommended for European patients (Kilonzo et al.,1994). To the best of the knowledge of the authors, derived from a review of recent metanalyses of trials for CMD and depression (Song et al.,1993; Hotopf et al.,1996) there are no published trials of the treatment of CMD in PHC attenders in low-income countries.

There have been very few studies on the use of antidepressants for CMD in India; those that have been published, such as the study by Singh & Sharma (1987), have used psychiatric outpatient samples. It is well recognized that the vast majority of patients with CMD only consult in primary care settings and findings from psychiatric settings may not be applicable to primary care. To date, there are no published randomized trials comparing the acceptability, efficacy and cost of low dose tricyclic, full-dose tricyclic and SSRI antidepressants in primary care settings in India. The overall aims of the study described in this paper were twofold : first, to establish whether there was any difference in tolerance between 3 widely used models of antidepressant treatments in primary care so that a choice could be made for a more subsantive trial evaluating efficacy in the future. Second, to examine the feasibility of conducting randomized trials of psychiatric treatments in primary care settings in India. The major limitation of this study is the small sample sizes in the 3 groups. This limitation must be taken into account when interpreting the finding of trends which are statistically non-significant but could be significant had the sample sizes been larger. It is our belief, given the significantly higher non-completion rates for the imipramine 150 group, that the trends would have been statistically significant were the samples larger. The second limitations is that discontinuation rates were so high that an intention to treat analysis for examining the difference in efficacy between the 3 groups was not feasible. All these limitations must however be considered in the light of the fact that this was a pilot study and that many of the limitations are in fact feasibility issues which will inform future trials.

The main findings of the trial are, first, that irrespective of the type or dose of antidepressant and despite the fact that the medication was free and considerable explanation was given to subjects as part of the informed consent procedure, discontinuation rates were high. Second, there was a higher discontinuation rate in the imipramine 150 mg group, mostly attributable to adverse effects of the drug. The commonest adverse effects which led to discontinuation were anticholinergic side effects and postural hypotension leading to giddiness. Thus, it is our view that the full dose of imipramine has limited value in general health care settings. There was no significant difference between imipramine 75 mg and fluoxetine 20 mg in terms of tolerance and discontinuation. It was noted that the discontinuation rates at 2 weeks were higher for the imipramine 150 mg group as compared to the imipramine 75 mg group even though, at this point in the trial, subjects in both groups were receiving the same dose of imipramine (50 mg). One possible

explanation for this apparent discrepancy is that subjects in the 75 mg group felt that they had already reached the maximum dose possible and were more accepting of the side effects they had experienced, whereas those who were in the 150 mg group were apprehensive that the expected increase in dosage would exacerbate their side effects. Given the fact that the commonest interventions currently used in general health care settings, viz., vitamins and other symptomaic treatments, are often considered to be "placebo" medicines, it would be of considerable interest to examine whether antidepressants are superior to these medications in a controlled trial. In particular, it would be of interest to compare discontinuation rates between drug and placebo. Thus, there is a need to conduct a substantive randomized placebo-controlled trial to examine the efficacy and cost-effectiveness of either fluoxetine 20 mg or imipramine 75 mg in primary or general health care settings.

In terms of the second objective of the trial, i.e. feasibility issues relating to randomized controlled trials, it is clear that the high discontinuation rates in all 3 groups due to side effects poses a major challenge to trials with antidepressants in general health care settings. Future trials will need to concentrate on improving compliance rates using sensitive education of patients regarding side effects, adequate monitoring using home visits and other forms of reminders as feasible and using drugs with the least side effects. The high discontinuation rates also challenges the notion that most primary care patients in India are prepared to take medication in preference to other options such as psychological treatments (though, to our knowledge, there have been no comparisons of these treatments in India). Thus, there is also a need to compare the acceptability and cost-effectiveness of pharmacological and psychological interventions in general health care. The second author is currently conducting a definitive placebo-controlled trial of antidepressant (fluoxetine chosen as a result of this pilot trial) and psychological treatment for comparison of efficacy and cost-effectiveness in general health care. Many of the lessons learned from this pilot trial are being used to attempt to improve compliance rates with treatments. The findings of that trial will be published in due course.

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