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Determination of appropriate clomipramine dosage among depressed African outpatients in Dar es Salaam, Tanzania

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SUMMARY

In an open clomipramine dose finding study, 33 depressed indigenous African outpatients were randomly assigned to two regimens of treatment with 125 mg and 75 mg oral medications daily. At the end of eight weeks of treatment, 16 patients (48,5 pc) were on the 75 mg regime, and 17 (54,8 pc) were on 125 mg.

Analysis of depression scores on the Beck-Rafaelsen scale indicated improvements of depression in both regimes of equal magnitude. Analysis of variance showed no statistically significant difference on dose response between the two regimes. The higher doses, however, were associated with more drowsiness and tremulousness.

It is suggested that Black African patients respond to tricyclic antidepressants in much lower doses than those recommended in Western textbooks. It is also apparent that side effects of tricyclic antidepressants, which have been implicated in non-compliance to medication, could be avoided without compromising treatment outcome.

INTRODUCTION

Ethnic and racial factors have been implicated as determinants to the outcome of psychotropic medication.[1,2] Ethnic differences in response to such medication affects dosage requirements and risk of potential side effects. Looking specifically at antidepressant medica-

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tion, significantly lower treatment and maintenance dosage requirements have been noted in Orientals when compared to Occidentals.[3] Patients were noted to respond equally to antidepressants regardless of the dosage chosen in Asia and other developing countries as opposed to the Occident where higher doses were effective.[4]

The majority of studies on Black populations have been done in the Americas and West Indies,[5,6] and tended to support the impression that Black patients with depression may respond to much lower doses of antidepressants than their Caucasian counterparts. This impression has also been supported by pharmacokinetics data, which indicated that Black patients have significantly higher nortriptyline plasma levels than White patients.[7] This finding may indicate different rates of metabolism which may be the explanation for the more rapid response among Blacks as well as response at lower dosage.

The different pharmacokinetics of drugs are thought to be related to a combination of genetic and environmental factors. Genetic differences in acetylation and oxidation have been implicated by Clark,[8] and this could explain the ethnic variability in dose response. Underlying psychogenic and biochemical factors in the aetiology of mental illness may also vary in different cultures, resulting in variations in symptomatology.[9]

The relevance of such differences to clinical practice, depends on the type of drug and costs involved. Drugs with narrow margins of safety, such as antidepressants, where unpleasant side effects may hamper compliance, make ethnic variability in response to treatment an important factor. Where funds for medical services are scarce, and purchasing of psychotherapeutic medications competes with drugs for highly prevalent infective conditions, as is the case in most developing countries, it is crucial to establish appropriate lowest effective dosage and not to employ the dosage established in Western cultures.

This study was designed to investigate whether Black depressed patients in Dar es Salaam could be successfully treated with clomipramine at lower doses than those in the West. The objectives of the study were to determine whether indigenous (Black) African patients suffering from depressive illness meeting the DSM-111 (American Psychiatric Association, 1980) criteria for condition responded to a lower dose of clomipramine than that recommended in standard textbooks, and whether such responses would be similar to those obtained with higher doses of the drug. The study also hoped to compare reported side effects amongst patients on a higher and lower dose regime of clomipramine. Such information would be useful in the training of mental health workers on appropriate dosage requirements to ensure not only adequate symptom relief, but also to mitigate against unpleasant side effects that may result in poor compliance.

MATERIALS AND METHODS

An open titration study design was used. Consecutive patients presenting with depression at new patients clinics of the Department of Psychiatry of Muhimbili Medical Centre over a nine month period beginning in April 1988 were recruited.

Inclusion criteria were:

1. A DSM-111 diagnosis for major depressive disorder.
2. Absence of any drug treatment for the current episode.
3. Indigenous African patient.
4. Age range between 16 and 70 years.

Patients were excluded if;

1. They had any cardiovascular, renal, or hepatic disorder.
2. The patient suffered from seizure disorder.
3. The patient was pregnant or planning pregnancy in the near future.
4. The patient suffered from or had a history of glaucoma.
5. There was a real possibility of poor compliance.
6. Neuroleptic medication would be necessary in addition to clomipramine.

Patients were withdrawn from the study if any of the exclusion criteria occurred during the course of treatment.

Informed consent was obtained prior to inclusion of the patients into the study and patients were randomized to the two dose regimens (Table I). On entry into the study, and at each follow up attendance, the patients' mood was rated using the Beck-Rafaelsen scale for depression. At follow up, if there was no change in more than half of the depressive scales listed, the patient was moved to the next higher dose in the particular regime.

Table I: Dose regimens A and B and time intervals for follow up visits.

Visits	Time interval from previous visit (days)	Dose A mg	Dose B mg
1	0	25	25
2	3	50	75
3	3	75	125
4	14	75	125
5	14	75	125
6	30	75	125

Four doctors were involved in the diagnosis of depression and rating of mood. One was a qualified psychiatrist and the rest residents in psychiatry. The principle investigator (GPK) counter checked all the diagnosis of depression.

Data analysis: Data entry and cleaning was done using Lotus 1-2-3 version 1.0 format before translation to SPSS-PC 2.0 for statistical analysis. Analysis of variance was carried out on the depression rating scores according to drug dosage during various visits.

Reliability of the depression scale: The Beck-Rafaelsen scale was studied by all the raters two weeks prior to the onset of the study. A day was spent clarifying issues and the scale tested out individually on patients by each of the raters prior to the second meeting. The initial 10 consecutive patients were rated separately by the principle investigator and a second rater to establish inter-rater reliability. Following this every fifth patient seen by each of the raters was re-rated by the principle investigator. An overall 95,1 pc agreement was achieved between raters and the principle investigator, ranging from between 94,6 pc and 96 pc.

RESULTS

Sixty four depressed patients meeting DSM-111 criteria for major depressive disorder with melancholia were seen and followed up over a two month period. Of these, 39 had no florid psychotic symptoms that would necessitate medication with neuroleptic drugs. Five patients refused to give consent and were not included in the study, while one patient was withdrawn due to non-compliance (failed to attend second follow up visit). Results are therefore reported on 33 patients, 12 females and 21 males.

There was no significant difference in the mean ages of male and female patients seen, 34,1 and 37,9 years respectfully (Table II). Just over a fifth (21,2 pc) of all the patients reported a family history of depressive illness, 12,1 pc reported a history of alcohol abuse, while 3 pc admitted abuse of other drugs. Characteristically, females tended to report a significantly longer duration of illness than males; 55,8 weeks as compared to 25,5 weeks ($p = 0,03$). No significant difference was noted in improvement, as judged by depression scores, when men and women were compared.

Table II: Distribution of the sample by sex and mean age within the two regimes.

Sex & age	Dose regime A	Dose regime B	Total
Males	11	10	21
Females	5	7	12
Total (pc)	48,5	51,5	100
Mean age (years)	37,7	31,2	34,4

When the patients assigned to dose regimes A and B were compared, no significant differences in age and sex distribution was noted, nor was there any difference in their mean depression scores on the first visit.

Due to the severity of depressive symptoms, three patients (9,1 pc) were started on 50 mg of clomipramine at the first visit. A decrease in depression score was noted as anticipated at each consecutive follow up visit, a larger drop occurring between one to five weeks of treatment (Table III). The largest decrease in mean depression score of about 3,5 pc was noted between the first and third week of treatment. At the end of the study period, 48,5 pc of patients were on 75 mg of clomipramine, while 51,5 pc of patients were on 125 mg.

Table III: Proportion of patients on different doses of clomipramine and mean depression score for the various visits.

Dose (mg)	Patients on various doses at each visit					
Visits	1	2	3	4	5	6
25	90,9					
50	9,1	36,7	10,7	3,0		
75		63,3	42,9	45,5	48,5	48,5
125			46,4	51,5	51,5	51,5
Mean depression score	18,7	17,6	14,1	11,5	8,96	7,17

Analysis of mean depression scores measured during each follow up visit at different drug dosage levels revealed reduction of scores with time at doses between 50 mg and 125 mg of clomipramine (Table IV). It was interesting that patients showing good responses to treatment on 50 mg of clomipramine, continued to show such improvement when maintained at that dose level on the third (four patients) and fourth (one patient) visits. No significant differences were noted in improvements of depression scores at 50 mg as compared to higher doses.

Table IV: Mean depression score during visits and different dosage levels.

	Dosage level (mg)				
Visits	25	50	75	125	p
1	19,0	11,0			< 0,5
2		18,6	17,2		< 0,5
3		17,3	14,0	13,4	< 0,5
4		14,0	11,8	11,1	< 0,5
5			9,1	8,8	< 0,5
6			7,9	6,5	< 0,5

Reduction of depressive symptoms, as evidenced by improvements in the depression scores, occurred in patients on both treatment regimes (Table V). In both regimes, a large drop in depression scores was noted between the second and third follow up visits. There was no statistical difference in dose response, as measured by depression scores over time, of patients in the two treatment groups.

Table V: Mean depression scores during visits comparing regimes A and B.

Visits	Regime A	Regime B	p
1	19,46	18,13	< 0,1
2	17,8	17,5	< 0,5
3	13,8	13,2	< 0,1
4	10,4	11,1	< 0,1
5	7,0	7,6	< 0,1
6	6,13	5,87	< 0,1

No clear pattern emerged when the side effects experienced by patients in the two regimes during the various follow up visits, was investigated. In total, 15 patients (45,5 pc) reported minor side effects following the first visit, while 26 patients (72,7 pc) reported side effects at the last visit. During the last visit, drowsiness was the most common complaint by patients on the higher dose regime followed by tremour, while constipation was reported more often by patients on the lower dose regime (Table VI). Although the number of patients reporting the different side effects were too small for valid statistical significance testing, the numbers reporting side effects were surprising, given that the doses used for this study were lower than those recommended by Western text books.

Table VI: Percentages of patients with side effects at first and sixth visit by the two treatment regimes.

Side effect	Visit 1 Regime		Visit 6 Regime	
	A	B	A	B
Dry mouth	15,25	9,1	0,0	0,0
Constipation	6,12	0,0	21,2	0,0
Tremor	0,0	3,0	0,0	9,1
Ataxia	6,1	0,0	0,0	0,0
Drowsiness	6,1	0,0	15,4	27,3

DISCUSSION

The small sample size in this study limits any broad generalizations, though as a preliminary inquiry into antidepressant dosage requirements of depressed Black African patients, it does reveal some information that supports anecdotal observations that depressed patients in this setting appear to respond to much lower doses of antidepressants than those recommended in textbooks.

These findings are especially significant given that depressed patients represent a large proportion of patients seen at primary health care levels. Hannah[10] identified depression in 29 pc of 1 100 patients, attending primary care facilities in three rural dispensaries in Tanzania, while depressed patients represent 18 pc of patients seen by community mental health teams in Dar es Salaam.[11] Holmes and Speight[12] noted that 48 pc of consecutive first attenders at a referral general medical clinic of a consultant hospital in Tanzania, primarily suffered from psychosocial conditions, a large proportion of which were depressive disorders. The use of lower doses of antidepressant medications would therefore contribute to a significant reduction in the cost of treatment.

Since the efficacy of clomipramine in depression is well established, and the main objective of the study

was to find out if lower doses were as effective as usual recommended doses, it was felt that an open trial would be sufficient at a preliminary inquiry into the subject of antidepressant dose requirements. The study relied on patients' and relatives' reports for assessment of compliance. Measurement of plasma clomipramine levels was not feasible because of scarcity of resources. However, consistency in the course of the clinical picture, suggested that compliance was good.

The results demonstrated that 75 mg clomipramine was as effective as 125 mg per day in the treatment of depression. There was also internal consistency of the results in that responses to the antidepressant effects of clomipramine, as evidenced by falling depression scores were in keeping with the clinical course of depression on tricyclic antidepressants. Although the small size of the sample made it difficult to interpret the significance of the occurrence of side effects, it appeared that higher doses were associated with more tremour while lower doses were associated with complaints of constipation.

As these results suggest, response to tricyclic antidepressants among Black Africans could occur with as low as 50 mg of clomipramine per day, and maintenance of this dose could result in further improvement of depressive scores as demonstrated by the four patients who were maintained on a daily dose of 50 mg. It might be possible to apply a very gradual increase in dose, carefully titrating clinical response with side effects, and in this way achieving better compliance without sacrificing clinical response.

The demonstration of response to antidepressant medication at lower than recommended doses in Black Africans is in keeping with studies done in Black depressed patients in North America[5,7] and the West Indies.[6] Socio-cultural factors in the west and the West Indies are very different from those in Tanzania. Biological factors (constitution and genetic) may explain the observed lower dose requirements among Black people. This aspect requires further studies which should include determination of plasma levels of clomipramine and enzymatic activity related to the metabolism of the drug in Black patients.

In conclusion, this study generally supports earlier findings of lower antidepressant requirements for Blacks compared to Caucasian patients suffering from depression. Given the unpleasant side effects of antidepressant medication, and the effect this might have on drug compliance, the authors advice that, Black African depressed patients should be started on low doses of antidepressants, which should then be gradually titrated against side effects, to arrive at an effective dose with fewer side effects.

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