Ethnicity and Treatment Response in Schizophrenia: A Comparison of 3 Ethnic Groups

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Background: Numerous cultural and ethnic factors may directly and indirectly influence treatment outcome in schizophrenia. The present study compared the response to antipsychotic treatment in 3 ethnic groups of patients with schizophrenia.

Method: Fifty black, 63 mixed descent, and 79 white patients with DSM-IV–diagnosed schizophrenia or schizophreniform disorder who were participants in multinational clinical drug trials were assessed by means of the Positive and Negative Syndrome Scale (PANSS). Treatment response was measured by the change in PANSS total scores and the change in positive, negative, and general psychopathology subscale scores from baseline to 6 weeks. Also, the percentage of responders (defined as ≥ 40% reduction in PANSS total scores) was calculated for each group.

Results: Baseline PANSS scores differed significantly, being higher for black and mixed descent patients. Mixed descent patients showed the greatest mean ± SD percentage reduction in PANSS total score (29.4 ± 21.6) followed by black (28.4 ± 14.7) and white (11.4 ± 27.6) patients. Analysis of covariance revealed a significant effect of ethnicity on the reduction in PANSS total scores ($p < .0001$). The numbers of responders were 20 mixed descent (32%), 12 black (24%), and 7 white (9%) patients ($p = .002$).

Conclusion: Significant ethnic differences in acute antipsychotic treatment response are demonstrated by this study. Factors such as diet, nutritional status, body mass, and substance use could be important, as well as genetically determined ethnospecific pharmacokinetic and pharmacodynamic differences. Delayed help-seeking may account for the higher baseline scores in the black and mixed descent patients.

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The field of ethnopsychopharmacology has become a focus of considerable attention. While psychotropic drugs appear to be effective across cultural and ethnic boundaries,[1,2] it is increasingly recognized that cross-cultural or cross-ethnic variations in responses to psychotropic agents do occur.[3,4] The discovery of widespread ethnospecific polymorphisms in genes governing pharmacokinetic and pharmacodynamic aspects of psychotropic drugs may explain some of these variations.[2,5] However, numerous other factors that are either directly or indirectly related to culture and ethnicity may be equally important. These include diet and nutritional status, exposure to various substances (e.g., alcohol, tobacco), body mass, accessibility of services, compliance, social support, and comorbid medical conditions.[6]

Differences in the doses of antipsychotics prescribed for the treatment of psychotic disorders in different ethnic groups have been consistently reported. African Americans are more likely than whites to receive higher doses.[7–13] This may in part be due to delayed help-seeking, greater body weight, or biased therapist attitudes.[11] Several retrospective studies have reported that Asian patients receive lower doses of antipsychotics than whites,[14–16] although one study[17] failed to find such differences. Also, Asians have been found to have higher plasma concentrations of antipsychotics than whites.[18,19] Ruiz et al.[20] examined a sample of 58 white, 135 African American, and 11 Hispanic patients who received conventional antipsychotics. The mean dose of antipsychotics was similar for the white and African American groups (16.2 and 15.5 mg of haloperidol equivalents/day, respectively), while for the Hispanic patients it was considerably lower (7.6 mg of haloperidol equivalents/day). In a similar study involving the atypical

antipsychotics (clozapine, risperidone, and olanzapine), African Americans were prescribed the highest mean doses, followed by Hispanics and whites. The doses prescribed for Asian Americans were much lower than for the other groups. These results may have been confounded by large differences that were found in mean body weights between the groups.[21]

While previous studies comparing ethnic differences in antipsychotic treatment have concentrated on examining the doses of antipsychotics prescribed, there is little information regarding the actual treatment responses of different ethnic groups. The present study compares the response to antipsychotic treatment in 3 ethnic groups of patients with schizophrenia and considers some factors that may contribute to differences in outcome.

METHOD

Subjects

Subjects were recruited from inpatient and outpatient hospital services. The study sample comprised patients who had participated in multinational randomized clinical trials from 2 academic psychiatric hospitals in South Africa (Stikland Hospital, Cape Town, and Oranje Hospital, Bloemfontein) where the Positive and Negative Syndrome Scale (PANSS)[22] had been used to assess symptom severity. They all met DSM-IV[23] criteria for schizophrenia or schizophreniform disorder and belonged to 1 of 3 ethnic groups: black, white, or mixed descent. Black patients were mainly from the Sotho (Sesotho and Setswana) ethnic group, with the rest from the Nguni group (Zulu and Xhosa). Mixed descent patients have developed from indigenous people living in the tip of Africa (San and Khoi), from slaves from Malaya and Madagascar, and from white European settlers.[24] White patients were largely of European descent. The trials were undertaken between 1991 and 2000. Subjects were men and women aged between 18 and 65 years, with no concomitant significant medical conditions, who did not meet criteria for substance abuse. All participants provided written, informed consent to participate in the clinical trials. Approval was obtained from the Ethics Committees of the Universities of Stellenbosch and Free State. The trials compared novel with conventional antipsychotics, and none had a placebo arm.

Ratings

All of the investigators were experienced psychiatrists who had undergone training and interrater reliability testing for the PANSS. Analyses were performed on the PANSS scores at baseline and at 6 weeks (or the closest assessment to 6 weeks that was performed, ranging from 5 to 9 weeks). The following PANSS scores were selected, according to previously specified criteria[22]: total PANSS score (30 items), positive subscale score (items P1–P7), negative subscale score (items N1–N7), and general psychopathology subscale score (items G1–G14). Treatment response was assessed by change from baseline to 6 weeks for PANSS total, positive subscale, negative subscale, and general psychopathology subscale scores. Also, the percentage of responders was calculated for each group. Responders were defined as those showing a 40% or greater reduction in PANSS total scores between baseline and 6 weeks.

Table 1. Mean ± SD Baseline Positive and Negative Syndrome Scale (PANSS) Scores for the Black, Mixed Descent, and White Subjects

	Black (N = 50)		Mixed Descent (N = 63)		White (N = 79)		F	p
Scale	Mean	SD	Mean	SD	Mean	SD	(df = 2,189)	Value
PANSS total	102.3	14.5	90.7	19.0	82.3	16.5	21.4	< .0001
PANSS positive	24.4	5.5	23.1	5.5	18.6	6.8	16.9	.0001
PANSS negative	27.6	4.8	24.8	7.8	24.8	5.8	3.56	.034
General psychopathology	50.3	8.5	42.8	10.3	38.9	8.7	23.6	< .0001
Composite score	–3.12	7.1	–1.7	9.1	–6.2	8.9	5.3	.006

Data Analysis

The chi-square test was used for comparing categorical variables. All tests were 2-tailed. For differences between groups, 1-way ANOVA or a chi-square test was performed where appropriate. To control for effects due to gender and age differences between the groups, ANCOVA was employed, with ethnicity and gender as categorical predictors and age as covariate. Tukey's honest significant difference test for unequal group sizes was used for post hoc pairwise comparisons. The significance level was set at .05.

RESULTS

The sample comprised 50 black, 63 mixed descent, and 79 white patients. The mean ± SD age of the mixed descent patients (29.3 ± 10.7 years) was significantly lower than that of the black patients (36.9 ± 9.9 years) ($p = .005$) and the white patients (38.6 ± 13.2 years) ($p < .0001$). The baseline PANSS scores for the 3 groups are given in Table 1. There were significant differences among the groups for all of the baseline PANSS scores. After controlling for age and gender, there was still a significant effect ($p < .001$) of ethnicity on baseline PANSS total scores ($F = 17.53$, $df = 2,189$), PANSS positive scores ($F = 11.3$, $df = 2,189$), and PANSS general psychopathology scores ($F = 21.04$, $df = 2,189$), but not the PANSS negative scores. Pairwise comparisons of PANSS total scores revealed significant differences between all ethnic groups ($p < .009$). The PANSS positive subscale scores for the white patients differed significantly from those for the mixed descent patients and black patients ($p < .0001$), and PANSS general psychopathology subscale scores differed significantly

Figure 1. Mean ± SE PANSS Total Scores for the 50 Black, 63 Mixed Descent, and 79 White Subjects at Baseline and After 6 Weeks of Treatment

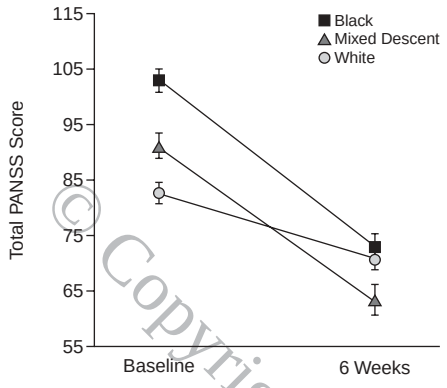


Figure 2. Mean ± SE PANSS Positive Subscale Scores for the 50 Black, 63 Mixed Descent, and 79 White Subjects at Baseline and After 6 Weeks of Treatment

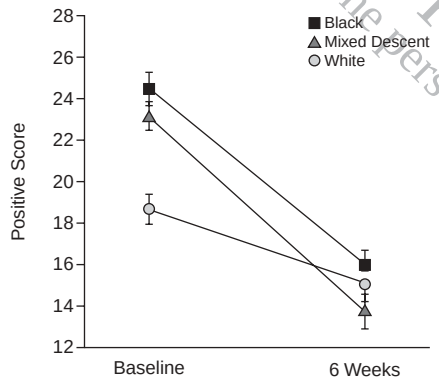


Figure 3. Mean ± SE PANSS Negative Subscale Scores for the 50 Black, 63 Mixed Descent, and 79 White Subjects at Baseline and After 6 Weeks of Treatment

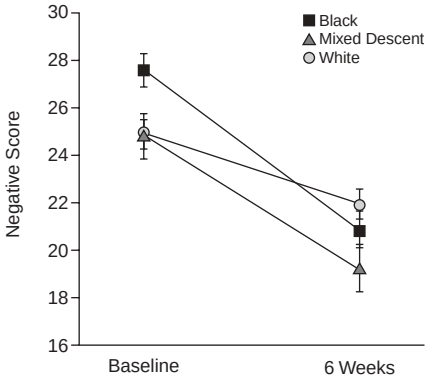
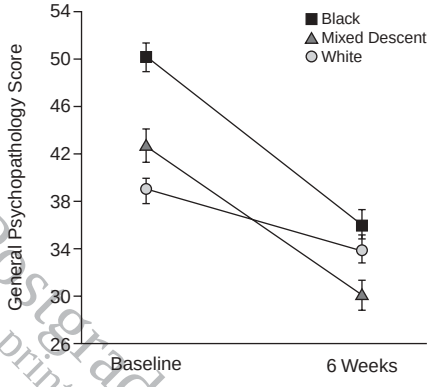


Figure 4. Mean ± SE PANSS General Psychopathology Subscale Scores for the 50 Black, 63 Mixed Descent, and 79 White Subjects at Baseline and After 6 Weeks of Treatment



between all 3 groups (black vs. white $p < .0001$; black vs. mixed descent $p = .004$; and mixed descent vs. white $p = .03$).

Figures 1 to 4 depict the change in PANSS total, positive, negative, and general psychopathology subscale scores between baseline and week 6. Although the black and mixed descent patients had significantly higher baseline PANSS total, positive, and general psychopathology subscale scores, their endpoint scores were similar to, and in some cases lower than, those for the white patients. Mixed descent patients showed the greatest percentage reduction in PANSS total scores (29.4 ± 21.6), followed by black patients (28.4 ± 14.7) and white patients (11.4 ± 27.6). Analysis of covariance, with ethnicity and age as categorical predictors and age as covariate, revealed a significant effect of ethnicity on percentage reduction in PANSS total scores ($F = 9.55$, $df = 2,189$; $p < .0001$). Pairwise comparisons showed that white patients differed significantly from mixed descent patients ($p < .0001$) and from black patients ($p = .008$), but that black and mixed descent patients did not ($p = .96$). The response rates (≥ 40% reduction in PANSS total scores) for each group were 20 mixed descent (32%), 12 black (24%), and 7 white (9%) patients ($\chi^2 = 12.2$, $df = 2$, $p = .002$).

DISCUSSION

This study demonstrates important ethnic differences in the acute response to antipsychotic treatment in patients with schizophrenia and schizophreniform disorder. Compared with white subjects, the mixed descent and black subjects showed a much greater reduction in symptoms and had significantly better response rates. Whether these differences in acute treatment response are maintained in the longer term and result in better overall outcome remains to be determined. This would appear to be likely,

though, as responsiveness to biological treatments is reported to be predictive of good outcome.[25] Also, initial reductions in positive and particularly negative symptoms are independently associated with reduced service use and improved quality of life after 2 years of treatment.[26]

There is considerable evidence to suggest that the clinical course of schizophrenia varies across cultures—the outcome in developing countries being generally more favorable[27]—although the evidence is not conclusive.[28] The reasons for these variations in outcome are not clear. While personal dynamics within the patient's family have been suggested as a major factor,[29] this is unlikely to account for the differences in acute treatment response that were observed in our study. Another possibility is that patients from certain cultural settings have a better outcome because they have fewer negative symptoms, which are less responsive to antipsychotic drugs. Once again, our findings do not support this hypothesis—the white subjects, who had the poorest outcome, did not have higher negative symptom scores. In fact, the baseline negative symptom scores of the black subjects were higher than, and those of the mixed descent subjects similar to, those of the whites, while the response for negative symptoms tended to be better in both black and mixed descent compared with white subjects.

The differences in treatment response could be partly explained by the differences in baseline PANSS scores, which in turn may be due to age differences—younger patients have been reported to have higher positive scores and a better response to antipsychotic treatment.[30] On the other hand, another study reported that high scores on both negative and positive subscales at index admission were significantly correlated with a *poor* outcome 5 years later.[31] Even after controlling for age in our study, the black and mixed descent patients had significantly higher baseline positive scores and better response to treatment than the white patients. Our findings therefore support previous work suggesting that there are real differences in responses to antipsychotics between ethnic groups.[7–12,16,20,21]

In addition to age differences, other factors could explain the higher baseline symptom scores for the mixed descent and black patients. For example, the illness may express itself differently across cultures, being less severe in some. We do not consider this likely, however, as most studies report the core symptoms of schizophrenia to be similar across cultures,[32–37] although a lower prevalence of first-rank or core symptoms has been found in developing countries,[38] in subjects less proficient in English,[39] and in minority groups,[40] while a higher prevalence of visual hallucinations has been reported in Kenyans.[41] Also, in a large sample of indigenous Africans, the factor structure for the symptoms of schizophrenia was found to be very similar to that previously described in white subjects.[42]

A more likely explanation for the differences in baseline scores is that there was a longer delay in help-seeking in the black and mixed descent subjects. Generally, treatment facilities are less accessible, and the level of community awareness of mental health matters is lower for blacks and mixed descents than it is for whites.[43] This is not a problem that is specific to South Africa—for example, in the United States, African Americans have limited access to the mental health system, and a variety of socioeconomic, cultural, attitudinal, and biological factors interact to preclude them from optimal care.[44] These patients are often treated differently—they are more likely to be hospitalized, involuntarily committed, placed in seclusion, and given depot antipsychotics.[44] These factors are thought to contribute to the reluctance of African Americans to utilize mental health services.

A number of factors could contribute to the observed differences in outcome between the ethnic groups, other than the already mentioned differences in baseline PANSS scores. For example, environmental factors such as differences in diet, nutritional status, body mass, and substance use and abuse may be important. These factors are known to affect the pharmacokinetics and pharmacodynamics of psychotropic drugs and may differ considerably between ethnic groups.[3,6] Apart from excluding substance abusers, none of these factors were investigated in this study. Finally, the possibility exists that genetically determined pharmacokinetic and pharmacodynamic differences exist between the ethnic groups. Further research will hopefully shed more light on this issue.

There are certain limitations to our study. First, there is a possibility of clinician bias, as the majority of investigators were white. Research has shown that the cultural and linguistic bias of the clinician has a significant influence upon the diagnosis and further management of the patient.[45] Clinicians, when dealing with patients whose cultural backgrounds are different from their own, run the risk of unwittingly applying an ethnocentric bias to their evaluation and treatment of these patients. This has been demonstrated to lead to inaccurate assessment and inadequate treatment.[10,46] It could be argued, for example, that the black and mixed descent groups contained some cases of "atypical psychoses," or bouffee delirante, known to be common in developing countries[47] and to have a favorable prognosis.[48] However, we consider this unlikely to be a major factor in our study, as the use of standard diagnostic procedures and rating scales has been shown to largely eliminate the possibility of cultural bias.[49]

Second, the study design did not make provision for examining the possible contributory effects of aspects such as diet, nutritional status, body mass, and duration of untreated psychosis. Third, the fact that patients received different antipsychotic drugs should be borne in mind, although the possibility of a treatment bias is minimized by the fact that the trials were randomized. Details of medication were not available to us, as some of the studies had not been unblinded at the time of our analysis. Fourth,

possible differences in chronicity and past treatment history could be important in explaining both baseline and outcome differences between the groups. Finally, it is not clear to what degree our findings can be generalized to other cultural settings.

This study confirms and extends previous work indicating ethnic differences in response to antipsychotic treatment. Substantial adjustments may be required in the prescribing habits of clinicians when dealing with patients of an ethnic group other than their own. Clinicians need to be alert to the many factors that may contribute directly and indirectly to cultural and ethnic variations in the response of patients to treatment. It may be that groups such as black and mixed descent groups require lower doses of antipsychotics than whites. It is of concern therefore that black patients generally receive higher doses than white patients, considering that they not only respond better, but may be more at risk for developing side effects such as tardive dyskinesia.[50] Future studies need to investigate factors such as body mass, nutritional status, and duration of symptoms before help is sought and include assessments of blood levels of antipsychotics, as well as the genetic structure of the drug-metabolizing enzymes in different ethnic groups. Although there are understandable sensitivities regarding research comparing different ethnic groups,[51] further such studies are clearly indicated.[52] Not only do differences in efficacy and tolerability need to be defined, but so too do inequities in service provision and social circumstances.

Drug names: clozapine (Clozaril and others), haloperidol (Haldol and others), olanzapine (Zyprexa), risperidone (Risperdal).

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