ORIGINAL RESEARCH ARTICLE

Drug Safety 2008; 31 (7): 597-607
0114-5916/08/0007-0597/$48.00/0

Ethnic Differences in the Risks of Adverse Reactions to Drugs Used in the Treatment of Psychoses and Depression

A Systematic Review and Meta-Analysis

Sara Ormerod,[1] *Sarah E. McDowell*,[2] *Jamie J. Coleman*[3] and *Robin E. Ferner*[2,3]

1 Queen Elizabeth Psychiatric Hospital, Birmingham, UK
2 West Midlands Centre for Adverse Drug Reactions, City Hospital, Birmingham, UK
3 Department of Clinical Pharmacology, University of Birmingham, Birmingham, UK

Abstract

Background: Factors such as age, sex and disease state alter a patient's susceptibility to adverse drug reactions (ADRs). Ethnicity may also alter the risk of an ADR.

Objective: To review the evidence for ethnic differences in susceptibility to adverse reactions to drugs used to treat psychoses and depression.

Data sources: We searched MEDLINE (from 1951), EMBASE (from 1974), and PsycINFO (from 1950) to March 2006.

Study selection: Studies were included if there was a mention of ethnicity, ethnic or racial groups and a description of a procedure to investigate ADRs specifically or a description of ADRs that were a result of drugs in therapeutic use. Studies selected by any two reviewers were retained if they referred to drugs used in the treatment of psychoses and related disorders or antidepressant drugs. Of 124 studies describing ADRs to antipsychotics or antidepressants, 51 reported data from different ethnic groups.

Data extraction: Data were extracted independently from those studies selected for inclusion by two reviewers, using a standard data extraction form. Studies were assessed for bias in order to determine the quality of the study.

Data synthesis: In a pooled analysis of patients treated with antipsychotics, the relative risk (RR) of tardive dyskinesia in Black compared with White patients was 1.03 (95% CI 0.85, 1.24); the RR of extrapyramidal symptoms in East Asian compared with non-East Asian patients was 1.38 (95% CI 1.11, 1.72); the RR of hyperglycaemia in Black compared with non-Black patients was 1.55 (95% CI 0.95, 2.53); and the RR of diabetes mellitus in non-White compared with White patients was 1.35 (95% CI 0.95, 1.92). It was impossible to perform pooled analysis of data from studies investigating antidepressants due to insufficient data.

Conclusions: We found limited evidence of ethnic differences in the risk of ADRs. The clinical implications of these results remain unclear because of confounding factors. Further progress will require improved recruitment of patients from different ethnic groups and an established consensus on how to define ethnicity.

Background

Adverse drug reactions (ADRs) are common and important.[1] ADRs to antipsychotic drugs are often conspicuous (e.g. movement disorders or weight gain) and can lead to stigmatization and poor compliance with treatment. A patient's susceptibility to ADRs depends on several factors, including age, sex, physiology, exogenous factors (such as concomitant drugs or diet) and disease state.[2] Genetic differences in pharmacokinetics and pharmacodynamics can alter a patient's risk of developing an ADR, and pharmacogenetic testing has been suggested as a way of personalizing drug treatment.[3] However, few pharmacogenetic tests have proven to be useful in clinical practice.[4]

Ethnicity could influence susceptibility to ADRs,[5] and drug efficacy.[6,7] Ethnic and racial classifications may reflect underlying genetics,[8] as there is some correlation between genetic data and geographical or continental ancestry.[9,10] However, the use of ethnicity in biomedical research is debatable because ethnic and racial categorizations may define heterogeneous groups and may be inaccurate representations of genetic variation.[11-13] Although they remain controversial, ethnic groupings may account for some of the complex interactions between genetics, environment and society.[14] These classifications remain socially meaningful, and are often used in studies on the treatment of patients. For example, in psychiatry, access to services, prognosis, admissions to hospital and treatment choice are all associated with ethnicity.[15,16]

This systematic review and meta-analysis aims to summarize what is known about the reported associations between ethnicity and ADRs from drugs used in the treatment of psychiatric disorders.

Methods

Search Strategy

In March 2006 we performed an extensive literature search without any language restrictions, identifying appropriate studies within the following databases: MEDLINE (from 1951), EMBASE (from 1974), and PsycINFO (from 1950). Relevant text words and search terms were used to identify papers containing both a description of ethnicity and ADRs in adults, excluding case reports or case series. Search terms of ADRs were exploded and appropriate free text words were included, and combined with a search strategy designed to identify studies with at least two ethnic groups.

Selection of Studies

Two reviewers (Jamie Coleman and Sarah McDowell) reviewed the title and abstract of all identified studies independently, using the following inclusion criteria:

- a mention of ethnicity, ethnic or racial groups; and
- a description of a procedure to investigate ADRs specifically, or a description of ADRs that were a result of drugs in therapeutic use.

A moderate level of agreement ($\kappa = 0.59$)[17] was obtained between the two reviewers. A third reviewer (R.E. Ferner) examined the studies identified for inclusion by only one person. Studies selected by any two reviewers were retained and where an ADR was described, the relevant drug was classified using the British National Formulary (BNF) classification.[18] Full-text copies of studies referring to drugs listed in BNF section 4.2 (drugs used in psychoses and related disorders) or 4.3 (antidepressant drugs) were obtained. Studies were included in the review if they contained comparative data for at least two ethnic groups and a defined ADR. Articles that cited or were cited by the included studies were also screened in order to identify any further relevant studies. We also searched personal files and reference lists from important reviews.

Two reviewers assessed each study independently for low, moderate or high risk of bias to provide an overall judgement of study validity and quality, specifically examining selection bias, performance bias, attrition bias and detection bias.[19]

Data Extraction

Data were extracted independently by two reviewers (Sara Ormerod and Sarah McDowell) from those studies selected for inclusion, using a standard data extraction form. Authors of papers where raw data were not available or who indicated there were no differences between ethnic groups were contacted and asked to provide the appropriate data. We

extracted data on ethnic groups as described in each paper using the authors' classification, although terms to describe ethnicity varied widely. To present the data using consistent terminology, where appropriate we used the following terms: 'Black' to describe a person with African ancestral origins, who self-identified, or was identified, as Black, African or African American; 'East Asian' to describe people whose ancestry was in Far East Asian countries (e.g. China, Japan and Korea); 'South Asian' to identify a person whose ancestry was in the countries of the Indian subcontinent; 'Hispanic' to describe a person of Latin American descent, who self-identified, or was identified, as Hispanic or Latino; 'White' to describe people with European ancestral origins who self-identified, or were identified, as White or Caucasian.[20]

Data Analysis

Studies were grouped by drug class and ADR. Heterogeneity between studies was estimated using the I^2 statistic,[21] and data were pooled by means of a fixed effects model if heterogeneity was absent, otherwise by means of a random effects model.[22] All analyses were carried out using Revman 4.2 (The Cochrane Collaboration, Oxford, UK).[23]

Results

The initial search strategy retrieved 4317 studies. Of these, 673 referred to ethnicity and ADRs, of which 124 related to antipsychotics and antidepressants. A total of 51 studies presented some comparative data and were analysed further (figure 1; see also supplementary material ['ArticlePlus'] at http://drugsafety.adisonline.com for more detail about the studies included).

Antipsychotic Drugs

Tardive Dyskinesia

Eleven studies investigated tardive dyskinesia (TD) – a late-onset ADR from prolonged exposure to antipsychotic treatment characterized by repetitive, involuntary, purposeless movements – in multi-ethnic patient groups. An early cross-sectional study suggested a difference in the prevalence of TD between Black and White patients treated with antipsychotics.[24] However, subsequent cross-sectional studies found no significant ethnic differences in the prevalence of TD.[25,26] Pooled analysis of the data from Black and White patients reported by the three medium quality studies suggests no difference in risk of TD (relative risk [RR] = 1.0; 95% CI 0.9, 1.2) [figure 2].

Six prospective studies of different size and length investigated the relationship between antipsychotics and TD in schizophrenic patients from multi-ethnic groups. Two studies reported a significantly increased risk of TD in Black compared with non-Black patients,[27,28] while four studies reported no ethnic difference.[29-32] None of the six studies provided raw data, each reported different adjusted outcomes, and therefore these studies could not be meta-analysed. Raw data from one study were obtained, but due to different classifications of ethnicity could not be included in the above pooled analysis.[32]

Two further cross-sectional studies in other ethnic groups were identified. The prevalence of TD did not differ significantly between Malay and Chinese patients treated with antipsychotics in one study,[33] or between patients in Israel and in India in another.[34]

Extrapyramidal Symptoms

Four small studies reported the incidence of extrapyramidal symptoms following treatment with antipsychotics in multi-ethnic populations. Extrapyramidal symptoms included acute dystonic reactions, parkinsonian rigidity and akathisia. Two studies[35,36] reported a significantly greater incidence of extrapyramidal symptoms in East Asian than in non-East Asian patients, but two other studies did not.[37,38] Pooled analysis of these four low-quality studies suggests that East Asian patients have a significantly greater risk of extrapyramidal symptoms compared with non-East Asian patients (RR = 1.4; 95% CI 1.1, 1.7) [figure 3].

In a fifth study of treatment with haloperidol, 16 East Asian psychiatric patients demonstrated significantly higher ratings for extrapyramidal symptoms on an ADR rating scale compared with 13 White patients.[39]

Hyperglycaemia

Three studies provided data on the development of hyperglycaemia in patients treated with atypical

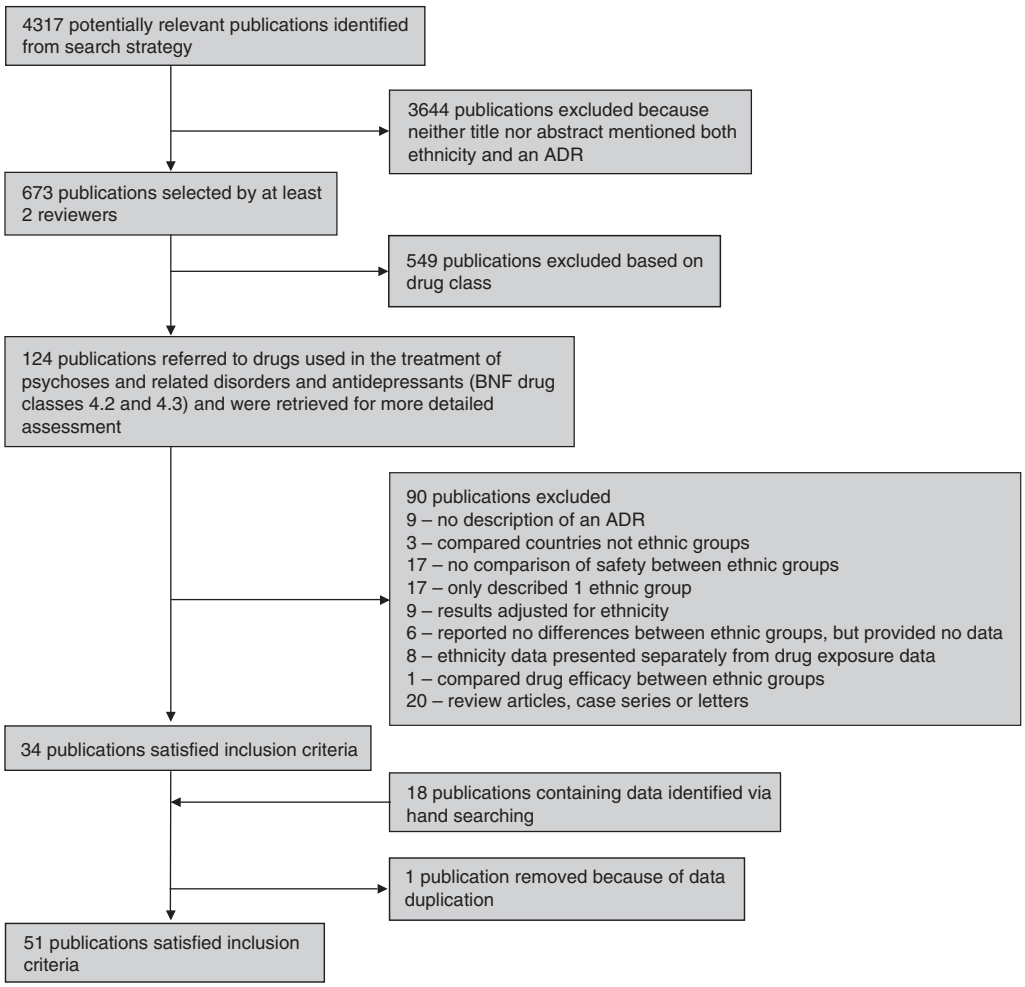

Fig. 1. Flowchart of study selection. **ADR** = adverse drug reaction; **BNF** = British National Formulary.

antipsychotics. In a masked clinical trial, 19% of Black patients displayed abnormally increased glucose concentrations, compared with 10% of White patients and no Hispanic patients.[40] There was no statistical difference between the ethnic groups. Two cross-sectional studies of patients treated with atypical antipsychotics in the same outpatient clinic over different time periods reported no statistically significant difference in the prevalence of hyperglycaemia between Black and non-Black patients.[41,42] Pooled analysis of these three medium quality studies indicates no statistically significant difference in the risk of hyperglycaemia between Black and non-Black patients (RR 1.6; 95% CI 0.95, 2.5) [figure 4].

Diabetes Mellitus

Five studies reported the risk of diabetes mellitus in different ethnic groups treated with antipsychotics. Compared with White patients, the odds ratio for diabetes mellitus in a 10-year naturalistic study[43] of clozapine treatment was 11.5 (95% CI 3.6, 36.9) in Black patients and 4.3 (95% CI 1.2, 15.6) in Hispanic patients. Non-White race was also associated with an increased risk of diabetes mellitus (OR 1.8; 95% CI 1.2, 2.6) in a 7-year retrospective analysis of antipsychotics[44] and in a study of clozapine (OR 3.6; 95% CI 1.2, 11.1).[45] No significant difference was demonstrated in a prospective study of atypical antipsychotics (χ^2 = 0.10;

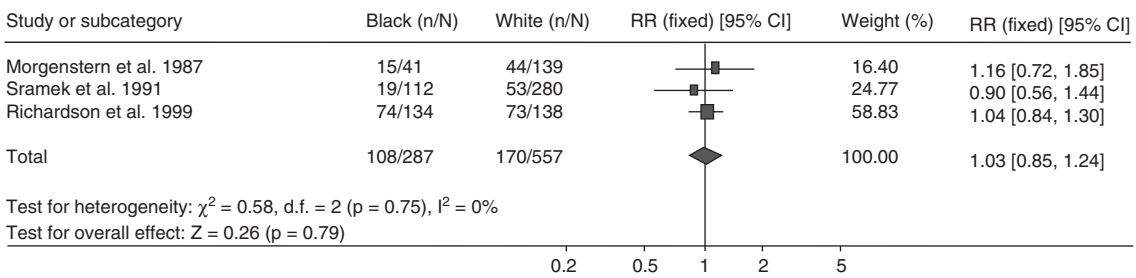

Fig. 2. Relative risk (RR) of tardive dyskinesia due to antipsychotics in Black patients compared with White patients. Studies: Morgenstern et al.,[24] Sramek et al.[25] and Richardson et al.[26] **d.f.** = degrees of freedom; **n** = number of patients with tardive dyskinesia; **N** = number of patients from each ethnic group in the study.

p = 0.75)[46] or in a retrospective study of atypical antipsychotics where 13% of White patients and 16% of non-White patients were found to have diabetes melliuts.[47] The increased risk of diabetes mellitus for non-White compared with White patients was not statistically significant in the three medium quality studies suitable for pooled analysis (RR 1.4; 95% CI 0.95, 1.9) [figure 5].[45-47]

Cardiovascular Events

The risk of cardiovascular mortality was increased in Black (OR 7.2; 95% CI 0.7, 69.9) and Hispanic patients (OR 11.3; 95% CI 1.1, 118.1) compared with White patients treated with antipsychotics in the one study identified.[43]

Metabolic Syndrome

A population study reported that the prevalence of metabolic syndrome in White and non-White patients treated with second-generation antipsychotics (39% vs 35%) did not differ significantly (p = 0.52).[48] However, hypertriglyceridaemia was more common in White patients than in non-White patients (46% vs 31%; p = 0.004).

Weight Gain

Three studies reported data on the association between weight gain, ethnicity and antipsychotic use. Non-White patients gained weight faster than White patients in a 2-year randomized masked clinical trial of olanzapine and haloperidol (hazard ratio 1.58; p = 0.01),[49] and significantly more weight in a 6-week clinical trial comparing olanzapine and haloperidol (p < 0.001);[50] there was no significant difference in weight gain (p = 0.154) between olanzapine and risperidone.[50] In an open-label trial of olanzapine in combination with fluoxetine, non-White patients were significantly less likely to gain weight (OR 0.495; p = 0.0202).[51]

Blood Disorders

We identified three studies that reported data on blood disorders following treatment with clozapine. South Asian patients were at higher risk of develop-

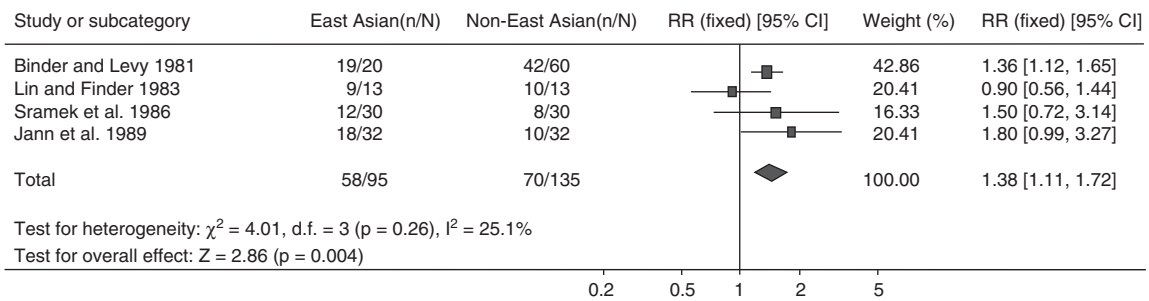

Fig. 3. Relative risk (RR) of extrapyramidal symptoms due to antipsychotics in East Asian compared with non-East Asian patients. Studies: Binder and Levy,[36] Lin and Finder,[37] Sramek et al.[38] and Jann et al.[35] **d.f.** = degrees of freedom; **n** = number of patients with extrapyramidal symptoms; **N** = number of patients from each ethnic group in the study.

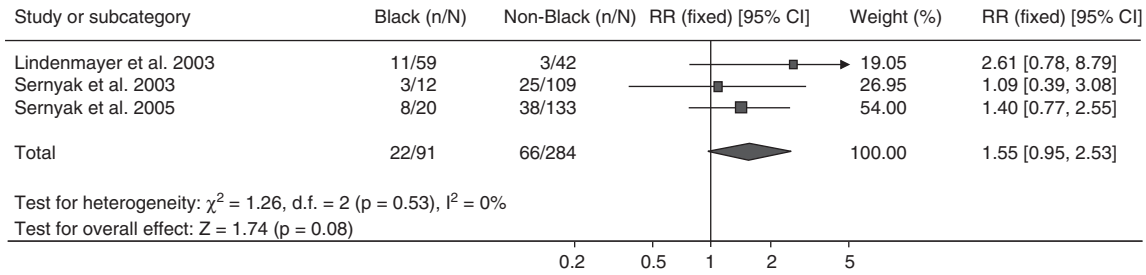

Fig. 4. Relative risk (RR) of hyperglycaemia due to antipsychotics in Black compared with non-Black patients. Studies: Lindenmayer et al.,[40] Sernyak et al.[42] and Sernyak et al.[41] **d.f.** = degrees of freedom; **n** = number of patients with hyperglycaemia; **N** = number of patients from each ethnic group in the study.

ing agranulocytosis (HR 2.4; 95% CI 1.1, 5.2) and Black patients had a 77% greater risk of neutropenia (HR 1.77; 95% CI 1.2, 2.6) than White patients.[52] Jewish Israeli patients of Ashkenazi descent were significantly more likely to show changes in total white blood cell counts than those of non-Ashkenazi descent, but rates of neutropenia and agranulocytosis were similar.[53,54]

Other Adverse Drug Reactions (ADRs)

Six studies reported associations between antipsychotics and general adverse effects or discontinuation due to ADRs. In a small cross-sectional study, 40% (12/30) of White patients treated with antipsychotics complained of general physical ADRs compared with 50% (10/20) of Black patients.[55] ADRs (headache, insomnia, agitation, psychosis, anxiety) were reported in 84% (119/141) of White, 80% (109/136) of Black and 80% (44/55) of patients classified as 'other' treated with risperidone in a masked, randomized, controlled trial.[56] In a placebo-controlled masked trial no significant differences were found between White and Black patients experiencing ADRs when treated with chlorpromazine.[57]

In one small clinical trial, East Asian patients were significantly more likely to experience anticholinergic ADRs to clozapine than White patients,[58] while in another they rated lower than White patients on an ADR scale.[59] The authors suggested greater chronicity of illness, more concomitant medication, or the lack of standardized rating training as explanations. Finally, a sixth study reported no significant difference between ethnic groups in the rates of discontinuation due to ADRs following treatment with clozapine.[60]

Drugs Used in Patients with Mania

Black patients had higher scores for fatigue, dizziness, loss of initiative, and urinary frequency, and overall on a general ADR scale than White patients treated with lithium.[61]

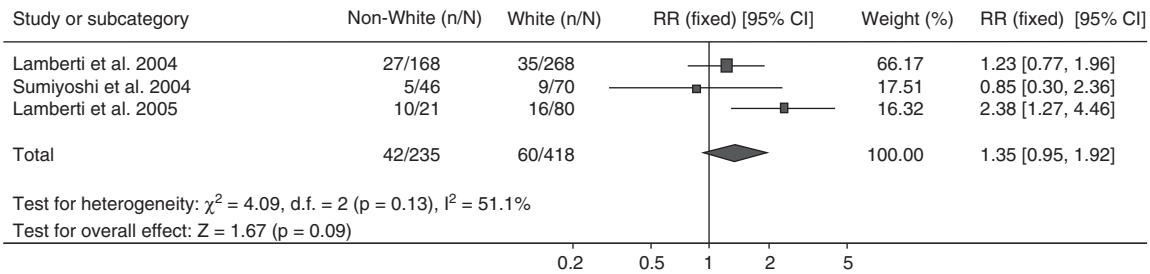

Fig. 5. Relative risk (RR) of diabetes mellitus due to antipsychotics in non-White compared with White patients. Studies: Lamberti et al.,[47] Sumiyoshi et al.[46] and Lamberti et al.[45] **d.f.** = degrees of freedom; **n** = number of patients with diabetes mellitus; **N** = number of patients from each ethnic group in the study.

Antidepressant Drugs

General ADRs

Five studies presented raw data on ADRs experienced by different ethnic groups treated with antidepressants. In a cross-sectional analysis of female outpatients, Hispanic patients experienced significantly more ADRs than White patients.[62] No significant differences were reported in a cross-sectional study that examined the influence of ethnicity on patients' expression of complaints to antidepressant therapy.[63] Likewise, an open-label trial of citalopram in 20 patients reported no significant differences in the number of Hispanic and non-Hispanic patients experiencing adverse events following treatment.[64] In a placebo-controlled trial of fluoxetine there was no significant ethnic difference in the prevalence of ADRs in a population of White, Black and Hispanic HIV-positive patients.[65] In a placebo-controlled masked trial of imipramine, ADRs did not differ between White and Black patients.[57]

Several small open-label trials monitored ADRs to antidepressants in different ethnic groups using various measurement scales. One reported that Hispanic patients had statistically significant higher scores than non-Hispanic patients,[66] while another, using a different scale, reported no differences among Hispanic, Black and White patients,[67] and a third reported no difference in the mean adverse effect score of elderly Black and Hispanic patients.[68]

The scores of East Asian and White patients on an ADR effect scale did not differ after 6 weeks of sertraline.[69] In a small clinical trial, South Asian volunteers had significantly greater mean ADR scores than White patients for two doses of clomipramine (25 mg and 50 mg).[70]

Specific ADRs

Livingston and colleagues identified delirium in a significantly greater number of Black than White patients receiving tricyclic antidepressants.[71]

In a cross-sectional study in primary care clinics, the prevalence of sexual dysfunction in patients receiving antidepressants did not differ significantly among five ethnic groups.[72]

Bailey and colleagues pooled safety data from seven masked, placebo-controlled, clinical trials of duloxetine.[73] The incidence of eight treatment-emergent ADRs was not significantly different between Black and White patients.

Pooled safety data from 104 masked, placebo-controlled clinical trials of paroxetine found no significant differences in 12 different ADRs between Black, Hispanic, East Asian and White patients.[74] However, insomnia was significantly more common in East Asian patients. It was impossible to perform pooled analyses from studies investigating antidepressants due to insufficient data from different ethnic groups.

Discussion

Ethnicity reflects components of both genetic and exogenous variability that are known to influence susceptibility to ADRs. We identified 51 publications that provided data on the occurrence of ADRs in different ethnic groups treated with antipsychotics and antidepressants. The data were heterogeneous and were presented in adjusted or different forms, which made synthesis of the results difficult. Pooled analysis suggested an increased risk of extrapyramidal symptoms in East Asian compared with non-East Asian patients treated with antipsychotics. Other ethnic differences in ADRs were inconsistent and less clear.

Ethnic differences in ADRs may stem from genetic differences in pharmacokinetic or pharmacodynamic factors. For example, the volume of distribution of a drug depends on body composition. A difference in body build was identified as one of the reasons for the greater effect of diazepam in East Asian compared with White patients.[75] East Asian patients have demonstrated significantly greater plasma haloperidol concentrations than White patients, as well as larger prolactin responses to haloperidol even after controlling for differences in haloperidol concentrations.[39,76] East Asians have a lower ratio of reduced haloperidol to haloperidol in plasma, which suggests that a lower rate of reduction may be responsible for the slower rate of metabolism.[35,77] These factors may therefore lead to an increase in the prevalence of ADRs in East Asians when given equivalent doses of specific antipsychotics. Furthermore, the HLA B38 phenotype, which occurs frequently in patients of Jewish Ashkenazi descent, and is associated with an in-

creased risk of agranulocytosis, provides another example.[54]

The relationship between ethnicity and increased susceptibility to ADRs may also be influenced by differences in the way in which adverse effects are described by patients of different ethnicity. Research has suggested that emotional distress is more often reported in terms of somatic sensations in some ethnic groups.[78,79] However, more recent research has suggested that somatization is widespread across countries and ethnic groups.[80,81]

We identified several studies that reported an increased risk of tardive dyskinesia in certain ethnic groups, particularly in Black patients. However, the data were inconsistent and any observed ethnic differences may have been due to underlying genetic differences or several extrinsic environmental factors. Research has demonstrated that Black patients are more likely to be diagnosed with schizophrenia than White patients and are more likely to receive higher doses of treatment.[82] Moreover, other research has shown that non-White patients are less likely to receive newer classes of antipsychotics.[83]

We also identified some studies that suggested ethnic differences in the occurrence of diabetes mellitus following treatment with antipsychotics. The data were inconsistent and results may be confounded by the difference in the prevalence of diabetes mellitus between different ethnic groups.[84-86] Furthermore, it was difficult to determine whether the exposure to antipsychotics preceded the development of diabetes mellitus.

Limitations

The data and results we have presented need to be interpreted with caution because the majority of the studies included in our analysis are limited by small sample size, lack of randomization, length of follow-up, and small numbers of non-White patients. The studies identified by the search strategy were also inconsistent in their reporting of ADRs and ethnicity, which made synthesis of results between studies difficult. Studies often did not describe how ethnic classifications were made, which limits the comparison between different studies. Because of limited data, it was sometimes necessary to combine ethnic groups to investigate possible associations between ethnicity and increased risk of ADRs. This may have obscured differences amongst larger ethnic groups, and limits the generalizability of the results. The use of consistent assignments to well-defined ethnic groups is necessary.[87]

Our results are also limited by the possibility that studies containing relevant data were overlooked. Even though our search strategy used a combination of indexing terms and text words, literature searches may fail to identify all studies that report data on ADRs.[88] Finally, because our search strategy was limited to published literature and excluded data from unpublished drug trials and conferences, this may have limited the available data.

Studies that identified differences in ADRs between ethnic groups may have been more likely to publish such data than studies where no such difference was found or where the analysis of the drug safety was not a primary study endpoint. This may have led to an overestimation of the association between ethnicity and ADRs.

The studies identified by our search strategy also did not present consistent data on possible confounding factors such as age, sex or exogenous diseases, so it was impossible to adjust any pooled analyses for these data. This may have resulted in an overestimate of the association between ethnicity and increased susceptibility to certain ADRs, as these factors have been shown to affect the risk of developing an ADR. Another confounding factor may have been variation in diagnosis of the adverse effect through differences in diagnostic criteria, particularly when the studies are carried out in different centres. This may have been a particular problem for some adverse reactions such as tardive dyskinesia.

Conclusions

Despite the drive to provide pharmacogenetic evidence for the basis of individualized treatments, there is a paucity of information about the genetics of ADRs. The studies we identified provided data on ethnicity but lacked concomitant genetic analysis. Ethnic classifications may be poor surrogates of underlying genetics, but they also take into account the environmental and cultural factors that operate both independently and synergistically with genetics

to affect drug response. Ethnic differences in increased susceptibility to ADRs may then act as markers for potentially important genetic or environmental factors that influence the balance of benefit and harm.

Our results illustrate that the evidence for ethnic differences in adverse reactions to antipsychotics and antidepressants is varied and inconsistent. While there is some evidence of increased susceptibility to certain ADRs in different ethnic groups, the results are limited by numerous factors including differences in the incidence of psychiatric disorders, incidence of certain conditions (e.g. diabetes), and in the expression of perceived ADRs in different populations. These data should not cause clinicians to become inappropriately cautious when prescribing some drugs to certain ethnic groups. Instead, these data highlight the need for further research in this area and may provide the impetus to direct research from population to molecular comparisons of differences in drug response.

In future, it is essential that authors are more explicit in the description of their ethnic classifications. Likewise, well-designed studies in multi-ethnic populations and increased recruitment of individuals from various ethnic groups are necessary. Future research which identifies correlations between ethnicity and ADRs may then assist professionals in personalizing treatment.

Acknowledgements

Sarah E. McDowell was supported by the Antidote Trust Fund of the Sandwell and West Birmingham Hospitals NHS Trust. The funding source had no role in the design and conduct of the study; collection, management, analysis and interpretation of the data; or preparation, review or approval of the manuscript. The authors have no conflicts of interest directly relevant to the content of this study.

References

1. Pirmohamed M, James S, Meakin S, et al. Adverse drug reactions as cause of admission to hospital: prospective analysis of 18 820 patients. BMJ 2004; 329 (7456): 15-9
2. Aronson JK, Ferner RE. Joining the DoTS: new approach to classifying adverse drug reactions. BMJ 2003; 327 (7425): 1222-5
3. Morley KI, Hall WD. Using pharmacogenetics and pharmacogenomics in the treatment of psychiatric disorders: some ethical and economic considerations. J Mol Med 2004; 82 (1): 21-30
4. Jaquenoud SE, van der Velden JW, Rentsch K, et al. Therapeutic drug monitoring and pharmacogenetic tests as tools in pharmacovigilance. Drug Saf 2006; 29 (9): 735-68
5. McDowell SE, Coleman JJ, Ferner RE. Systematic review and meta-analysis of ethnic differences in risks of adverse reactions to drugs used in cardiovascular medicine. BMJ 2006; 332 (7551): 1177-81
6. Xie HG, Kim RB, Wood AJ, et al. Molecular basis of ethnic differences in drug disposition and response. Annu Rev Pharmacol Toxicol 2001; 41: 815-50
7. Bjornsson TD, Wagner JA, Donahue SR, et al. A review and assessment of potential sources of ethnic differences in drug responsiveness. J Clin Pharmacol 2003; 43 (9): 943-67
8. Tate SK, Goldstein DB. Will tomorrow's medicines work for everyone? Nat Genet 2004; 36 (11 Suppl.): 34-S42
9. Jorde LB, Wooding SP. Genetic variation, classification and 'race'. Nat Genet 2004; 36 (11 Suppl.): 28-S33
10. Daar AS, Singer PA. Pharmacogenetics and geographical ancestry: implications for drug development and global health. Nat Rev Genet 2005; 6 (3): 241-6
11. Schwartz RS. Racial profiling in medical research. N Engl J Med 2001; 344 (18): 1392-3
12. Wilson JF, Weale ME, Smith AC, et al. Population genetic structure of variable drug response. Nat Genet 2001; 29 (3): 265-9
13. Cooper RS, Kaufman JS, Ward R. Race and genomics. N Engl J Med 2003; 348 (12): 1166-70
14. Risch N, Burchard E, Ziv E, et al. Categorization of humans in biomedical research: genes, race and disease. Genome Biol 2002; 3 (7): 1-12
15. McKenzie K, Samele C, Van Horn E, et al. Comparison of the outcome and treatment of psychosis in people of Caribbean origin living in the UK and British Whites: report from the UK700 trial. Br J Psychiatry 2001; 178: 160-5
16. Morgan C, Mallett R, Hutchinson G, et al. Pathways to care and ethnicity: 1, sample characteristics and compulsory admission -report from the AESOP study. Br J Psychiatry 2005; 186: 281-9
17. Landis JR, Koch GG. The measurement of observer agreement for categorical data. Biometrics 1977; 33 (1): 159-74
18. British National Formulary. No. 50, 50th edition. London: British Medical Association and the Royal Pharmaceutical Society of Great Britain, 2005
19. Higgins J, Green S. Assessment of study quality. Cochrane handbook for systematic reviews of interventions 4.2.5. Chichester: The Cochrane Collaboration, 2005
20. Bhopal R. Glossary of terms relating to ethnicity and race: for reflection and debate. J Epidemiol Community Health 2004; 58 (6): 441-5
21. Higgins JP, Thompson SG, Deeks JJ, et al. Measuring inconsistency in meta-analyses. BMJ 2003; 327 (7414): 557-60
22. Egger M, Smith GD, Phillips AN. Meta-analysis: principles and procedures. BMJ 1997; 315 (7121): 1533-7
23. Review Manager (RevMan). Oxford: The Cochrane Collaboration, 2002
24. Morgenstern H, Glazer WM, Gibowski LD, et al. Predictors of tardive dyskinesia: results of a cross-sectional study in an outpatient population. J Chronic Dis 1987; 40 (4): 319-27
25. Sramek J, Roy S, Ahrens T, et al. Prevalence of tardive dyskinesia among three ethnic groups of chronic psychiatric patients. Hosp Community Psychiatry 1991; 42 (6): 590-2
26. Richardson MA, Reilly MA, Read LL, et al. Phenylalanine kinetics are associated with tardive dyskinesia in men but not in women. Psychopharmacology (Berl) 1999; 143 (4): 347-57
27. Morgenstern H, Glazer WM. Identifying risk factors for tardive dyskinesia among long-term outpatients maintained with

neuroleptic medications: results of the Yale Tardive Dyskinesia Study. Arch Gen Psychiatry 1993; 50 (9): 723-33
28. Van Os J, Fahy T, Jones P, et al. Tardive dyskinesia: who is at risk? Acta Psychiatr Scand 1997; 96 (3): 206-16
29. Jeste DV, Caligiuri MP, Paulsen JS, et al. Risk of tardive dyskinesia in older patients: a prospective longitudinal study of 266 outpatients. Arch Gen Psychiatry 1995; 52 (9): 756-65
30. Chakos MH, Alvir JM, Woerner MG, et al. Incidence and correlates of tardive dyskinesia in first episode of schizophrenia. Arch Gen Psychiatry 1996; 53 (4): 313-9
31. Van Os J, Walsh E, Van Horn E, et al. Changes in negative symptoms and the risk of tardive dyskinesia: a longitudinal study. UK700 Group. Acta Psychiatr Scand 2000; 101 (4): 300-6
32. Oosthuizen PP, Emsley RA, Maritz JS, et al. Incidence of tardive dyskinesia in first-episode psychosis patients treated with low-dose haloperidol. J Clin Psychiatry 2003; 64 (9): 1075-80
33. Chong SA, Mahendran R, Machin D, et al. Tardive dyskinesia among Chinese and Malay patients with schizophrenia. J Clin Psychopharmacol 2002; 22 (1): 26-30
34. Bhatia T, Sabeeha MR, Shriharsh V, et al. Clinical and familial correlates of tardive dyskinesia in India and Israel. J Postgrad Med 2004; 50 (3): 167-72
35. Jann MW, Chang WH, Davis CM, et al. Haloperidol and reduced haloperidol plasma levels in Chinese vs. non-Chinese psychiatric patients. Psychiatry Res 1989; 30 (1): 45-52
36. Binder RL, Levy R. Extrapyramidal reactions in Asians. Am J Psychiatry 1981; 138 (9): 1243-4
37. Lin KM, Finder E. Neuroleptic dosage for Asians. Am J Psychiatry 1983; 140 (4): 490-1
38. Sramek JJ, Sayles MA, Simpson GM. Neuroleptic dosage for Asians: a failure to replicate. Am J Psychiatry 1986; 143 (4): 535-6
39. Lin KM, Poland RE, Nuccio I, et al. A longitudinal assessment of haloperidol doses and serum concentrations in Asian and Caucasian schizophrenic patients. Am J Psychiatry 1989; 146 (10): 1307-11
40. Lindenmayer JP, Czobor P, Volavka J, et al. Changes in glucose and cholesterol levels in patients with schizophrenia treated with typical or atypical antipsychotics. Am J Psychiatry 2003; 160 (2): 290-6
41. Sernyak MJ, Gulanski B, Rosenheck R. Undiagnosed hyperglycemia in patients treated with atypical antipsychotics. J Clin Psychiatry 2005; 66 (11): 1463-7
42. Sernyak MJ, Gulanski B, Leslie DL, et al. Undiagnosed hyperglycemia in clozapine-treated patients with schizophrenia. J Clin Psychiatry 2003; 64 (5): 605-8
43. Henderson DC, Nguyen DD, Copeland PM, et al. Clozapine, diabetes mellitus, hyperlipidemia, and cardiovascular risks and mortality: results of a 10-year naturalistic study. J Clin Psychiatry 2005; 66 (9): 1116-21
44. Barner JC, Worchel J, Yang M. Frequency of new-onset diabetes mellitus and use of antipsychotic drugs among Central Texas veterans. Pharmacotherapy 2004; 24 (11): 1529-38
45. Lamberti JS, Costea GO, Olson D, et al. Diabetes mellitus among outpatients receiving clozapine: prevalence and clinical-demographic correlates. J Clin Psychiatry 2005; 66 (7): 900-6
46. Sumiyoshi T, Roy A, Anil AE, et al. A comparison of incidence of diabetes mellitus between atypical antipsychotic drugs: a survey for clozapine, risperidone, olanzapine, and quetiapine. J Clin Psychopharmacol 2004; 24 (3): 345-8
47. Lamberti JS, Crilly JF, Maharaj K, et al. Prevalence of diabetes mellitus among outpatients with severe mental disorders receiving atypical antipsychotic drugs. J Clin Psychiatry 2004; 65 (5): 702-6
48. Correll CU, Frederickson AM, Kane JM, et al. Metabolic syndrome and the risk of coronary heart disease in 367 patients treated with second-generation antipsychotic drugs. J Clin Psychiatry 2006; 67 (4): 575-83
49. Zipursky RB, Gu H, Green AI, et al. Course and predictors of weight gain in people with first-episode psychosis treated with olanzapine or haloperidol. Br J Psychiatry 2005; 187: 537-43
50. Basson BR, Kinon BJ, Taylor CC, et al. Factors influencing acute weight change in patients with schizophrenia treated with olanzapine, haloperidol, or risperidone. J Clin Psychiatry 2001; 62 (4): 231-8
51. Andersen SW, Clemow DB, Corya SA. Long-term weight gain in patients treated with open-label olanzapine in combination with fluoxetine for major depressive disorder. J Clin Psychiatry 2005; 66 (11): 1468-76
52. Munro J, O'Sullivan D, Andrews C, et al. Active monitoring of 12,760 clozapine recipients in the UK and Ireland: beyond pharmacovigilance. Br J Psychiatry 1999; 175: 576-80
53. Meged S, Stein D, Sitrota P, et al. Human leukocyte antigen typing, response to neuroleptics, and clozapine-induced agranulocytosis in Jewish Israeli schizophrenic patients. Int Clin Psychopharmacol 1999; 14 (5): 305-12
54. Lieberman JA, Yunis J, Egea E, et al. HLA-B38, DR4, DQw3 and clozapine-induced agranulocytosis in Jewish patients with schizophrenia. Arch Gen Psychiatry 1990; 47 (10): 945-8
55. Fleck DE, Keck Jr PE, Corey KB, et al. Factors associated with medication adherence in African American and white patients with bipolar disorder. J Clin Psychiatry 2005; 66 (5): 646-52
56. Ciliberto N, Bossie CA, Urioste R, et al. Lack of impact of race on the efficacy and safety of long-acting risperidone versus placebo in patients with schizophrenia or schizoaffective disorder. Int Clin Psychopharmacol 2005; 20 (4): 207-12
57. Raskin A, Crook TH. Antidepressants in black and white inpatients: differential response to a controlled trial of chlorpromazine and imipramine. Arch Gen Psychiatry 1975; 32 (5): 643-9
58. Matsuda KT, Cho MC, Lin KM, et al. Clozapine dosage, serum levels, efficacy, and side-effect profiles: a comparison of Korean-American and Caucasian patients. Psychopharmacol Bull 1996; 32 (2): 253-7
59. Ng CH, Chong SA, Lambert T, et al. An inter-ethnic comparison study of clozapine dosage, clinical response and plasma levels. Int Clin Psychopharmacol 2005; 20 (3): 163-8
60. Moeller FG, Chen YW, Steinberg JL, et al. Risk factors for clozapine discontinuation among 805 patients in the VA hospital system. Ann Clin Psychiatry 1995; 7 (4): 167-73
61. Strickland TL, Lin KM, Fu P, et al. Comparison of lithium ratio between African-American and Caucasian bipolar patients. Biol Psychiatry 1995; 37 (5): 325-30
62. Marcos LR, Cancro R. Pharmacotherapy of Hispanic depressed patients: clinical observations. Am J Psychother 1982; 36 (4): 505-12
63. Sleath B, Rubin RH, Wurst K. The influence of Hispanic ethnicity on patients' expression of complaints about and problems with adherence to antidepressant therapy. Clin Ther 2003; 25 (6): 1739-49
64. Currier MB, Molina G, Kato M. Citalopram treatment of major depressive disorder in Hispanic HIV and AIDS patients: a prospective study. Psychosomatics 2004; 45 (3): 210-6
65. Wagner GJ, Maguen S, Rabkin JG. Ethnic differences in response to fluoxetine in a controlled trial with depressed HIV-positive patients. Psychiatr Serv 1998; 49 (2): 239-40
66. Alonso M, Val E, Rapaport MH. An open-label study of SSRI treatment in depressed hispanic and non-Hispanic women [letter]. J Clin Psychiatry 1997; 58 (1): 31
67. Diaz E, Woods SW, Rosenheck RA. Effects of ethnicity on psychotropic medications adherence. Community Ment Health J 2005; 41 (5): 521-37

68. Ayalon L, Arean PA, Alvidrez J. Adherence to antidepressant medications in black and Latino elderly patients. Am J Geriatr Psychiatry 2005; 13 (7): 572-80
69. Ng CH, Norman TR, Naing KO, et al. A comparative study of sertraline dosages, plasma concentrations, efficacy and adverse reactions in Chinese versus Caucasian patients. Int Clin Psychopharmacol 2006; 21 (2): 87-92
70. Allen JJ, Rack PH, Vaddadi KS. Differences in the effects of clomipramine on English and Asian volunteers: preliminary report on a pilot study. Postgrad Med J 1977; 53 Suppl. 4: 79-86
71. Livingston RL, Zucker DK, Isenberg K, et al. Tricyclic antidepressants and delirium. J Clin Psychiatry 1983; 44 (5): 173-6
72. Clayton AH, Pradko JF, Croft HA, et al. Prevalence of sexual dysfunction among newer antidepressants. J Clin Psychiatry 2002; 63 (4): 357-66
73. Bailey RK, Mallinckrodt CH, Wohlreich MM, et al. Duloxetine in the treatment of major depressive disorder: comparisons of safety and efficacy. J Natl Med Assoc 2006; 98 (3): 437-47
74. Roy-Byrne PP, Perera P, Pitts CD, et al. Paroxetine response and tolerability among ethnic minority patients with mood or anxiety disorders: a pooled analysis. J Clin Psychiatry 2005; 66 (10): 1228-33
75. Kumana CR, Lauder IJ, Chan M, et al. Differences in diazepam pharmacokinetics in Chinese and white Caucasians: relation to body lipid stores. Eur J Clin Pharmacol 1987; 32 (2): 211-5
76. Lin KM, Poland RE, Lau JK, et al. Haloperidol and prolactin concentrations in Asians and Caucasians. J Clin Psychopharmacol 1988; 8 (3): 195-201
77. Chang WH, Chen TY, Lee CF, et al. Low plasma reduced haloperidol/haloperidol ratios in Chinese patients. Biol Psychiatry 1987; 22 (11): 1406-8
78. Nikelly AG. Does DSM-III-R diagnose depression in non-Western patients? Int J Soc Psychiatry 1988; 34 (4): 316-20
79. Mumford DB. Detection of psychiatric disorders among Asian patients presenting with somatic symptoms. Br J Hosp Med 1992; 47 (3): 202-4
80. Kirmayer LJ, Young A. Culture and somatization: clinical, epidemiological, and ethnographic perspectives. Psychosom Med 1998; 60 (4): 420-30
81. Simon GE, VonKorff M, Piccinelli M, et al. An international study of the relation between somatic symptoms and depression. N Engl J Med 1999; 341 (18): 1329-35
82. Ruiz P, Varner RV, Small DR, et al. Ethnic differences in the neuroleptic treatment of schizophrenia. Psychiatr Q 1999; 70 (2): 163-72
83. Opolka JL, Rascati KL, Brown CM, et al. Ethnicity and prescription patterns for haloperidol, risperidone, and olanzapine. Psychiatr Serv 2004; 55 (2): 151-6
84. National Center for Chronic Disease Prevention and Health Promotion. Age-adjusted prevalence of diagnosed diabetes per 100 population, by race/ethnicity and sex, United States, 1980–2005 [online]. Available from URL: http://www.cdc.gov/diabetes/statistics/prev/national/tableraceethsex.htm [Accessed 2006 Apr 11]
85. The Information Centre. Health survey for England 2004: health of ethnic minorities. Leeds: The Information Centre, 2006
86. Shai I, Jiang R, Manson JE, et al. Ethnicity, obesity, and risk of type 2 diabetes in women: a 20-year follow-up study. Diabetes Care 2006; 29 (7): 1585-90
87. International Committee of Medical Journal Editors. Uniform requirements for manuscripts submitted to biomedical journals: writing and editing for biomedical publication [online]. Available from URL: http://www.icmje.org/#prepare [Accessed 2006 Apr 11]
88. Derry S, Kong LY, Aronson JK. Incomplete evidence: the inadequacy of databases in tracing published adverse drug reactions in clinical trials. BMC Med Res Methodol 2001; 1: 7

Correspondence: Professor *Robin E. Ferner*, West Midlands Centre for Adverse Drug Reactions, City Hospital, Dudley Road, Birmingham, B18 7QH, UK.
E-mail: r.e.ferner@bham.ac.uk