

# Ethnopsychopharmacology: Clinical and scientific writing pearls

Jonathan G. Leung, PharmD, BCPS, BCPP<sup>1</sup>

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## Abstract

The concept of ethnopsychopharmacology aims to predict or explain the pharmacologic response to psychiatric medications based on the influence of biologic and nonbiologic factors. Interactions involving these factors are complex and influence patient outcomes in health care. Pharmacists and other clinicians working in patient care environments, research, or medical education should engage in lifelong learning to enhance ethnopsychopharmacologic knowledge gaps, which ultimately may improve and individualize care across diverse populations. Through two cases, this paper provides pearls on how biogeographical ancestry and cytochrome P450 status may influence pharmacotherapy selection, dosing, or response. A third scenario highlights a publication, like many other published works, with deficiencies in how data on ancestry, race, and ethnicity are collected or reported. Current recommendations on the use of inclusive language in scientific writing are reviewed, with attention to specific examples.

**Keywords:** ethnopsychopharmacology, antipsychotics, antidepressants, pharmacogenomics, precision medicine, clozapine

<sup>1</sup>(Corresponding author) Pharmacist, Mayo Clinic, Rochester, Minnesota, [leung.jonathan@mayo.edu](mailto:leung.jonathan@mayo.edu), ORCID: <https://orcid.org/0000-0003-3836-9375>

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## Introduction

Ethnopsychopharmacology is a concept that calls attention to the variability in psychiatric medication responses from the influences of biologic factors (eg, genetics) and nonbiologic factors (eg, race, ethnicity, lived experiences, cultural influences, environment, history, and societal influences).<sup>1,2</sup> Genetic ancestry is related to the biological inheritance of genetic material that provides information about an individual's lineage and may be referred to as continental ancestry.<sup>3-5</sup> Race and ethnicity, considered social constructs, should not

be used in isolation as surrogates for genetic ancestry to explain biologic variation or outcomes.<sup>3,6</sup> However, the use of race and ethnicity can be appropriate in the context of other sociodemographic factors to identify and address inequities such as access to psychiatric care, quality of care, or social determinants of health.<sup>3,7</sup> At the individual-patient level, pharmacists and other health care professionals should take an interest in understanding how medication outcomes are impacted by nonbiologic factors. This may include awareness of a patient's developed perceptions of health care, societal stigmas that affect the acceptance of psychiatric treatment, patients' expectations of psychiatric treatment, or the presence of barriers to optimal adherence. While acknowledging the importance of nonbiologic factors, two pearls here focus on select biologic ethnopsychopharmacology factors, including genetic ancestry and cytochrome P450 (CYP) polymorphisms. A third pearl will address the complexities, overlap, and sometimes ambiguous use of race, ethnicity, and genetic ancestry in the medical literature. Recommendations and specific examples of appropriate verbiage, interpretation, and application of relevant terms are reviewed to promote inclusive language. In all, it should be noted that while cases can provide context to broader themes and be explained with targeted evidence, readers should take the initiative to explore additional information to support their practice. The desire

## Take Home Points:

1. Clinicians should consider how ancestry may influence medication dosing, the risk for adverse drug reactions, and treatment outcomes.
2. While widespread pharmacogenomic testing is not yet considered standard practice in psychiatry, recognizing ancestry trends of differing cytochrome P450 phenotypes might be helpful in predicting or explaining medication-related outcomes in some cases.
3. Clinicians, researchers, and medical educators should be aware of the evolving use of language to promote inclusivity in practice or scientific writing. Familiarity with the *AMA Manual of Style: A Guide for Authors and Editors*, the *NIH Style Guide*, or other relevant up-to-date resources can be helpful in directing the use of race and ethnicity terminology in scientific publications.

for ongoing self-learning is crucial given the ever-changing nature and understanding of these topics.

### Case 1: Genetic Ancestry and Clozapine

A 31-year-old, nonsmoking Cambodian man with a history of schizophrenia was admitted to an inpatient psychiatric unit for worsening psychosis after missing an unknown number of monthly paliperidone palmitate injections. He was restarted on oral paliperidone and transitioned to 234 mg of intramuscular paliperidone palmitate every month during the hospitalization. Due to ongoing psychotic symptoms, the plan was to initiate clozapine and continue paliperidone palmitate. Clozapine at 12.5 mg at bedtime was started, increasing by 12.5 mg daily to 50 mg by day 4. Subsequent clozapine increases occurred by 25 mg per day until reaching 200 mg on day 10. By this time, the patient had developed constipation managed with polyethylene glycol and sialorrhea treated with 1% atropine ophthalmic drops administered sublingually. Following the fourth day of clozapine at 200 mg, the patient developed a fever of 40°C, tachycardia, tachypnea, hypotension, and altered mental status. Clozapine and norclozapine serum concentrations were obtained (approximately 12 hours postdose) and would be reported as 789 ng/mL and 166 ng/mL, respectively. The C-reactive protein (CRP) concentration also collected at this time was 32.3 mg/L, reaching 78.6 mg/L four days later. Troponins were negative, and there was no neutropenia. Upon examination, there was no rigidity, tremor, or reported myalgias. The creatine kinase concentration was within normal limits. Clozapine and paliperidone palmitate (injected approximately 1 month previously) were held, and the patient was transferred to a medical unit for further evaluation. Computed tomography showed an infiltrate in the right

upper lobe and left lower lobe, consistent with pneumonia. Eosinophilia developed 3 days after the medical transfer, peaking at 1170/ $\mu$ L before normalizing 2 days later. He was diagnosed with sepsis secondary to methicillin-sensitive *Staphylococcus aureus* pneumonia and transferred back to the inpatient psychiatry unit after clinical improvement. While clozapine reinitiation was considered, the patient was not amenable to that plan, and it would not be restarted.

### Ethnopsychopharmacology in Practice

The concept of ethnopsychopharmacology is not novel and may date back to at least the 1970s, with reports that patients from China required lower doses of tricyclic antidepressants and experienced greater side effects than White patients from Australia.<sup>2</sup> Unfortunately, the research and literature written on ethnopsychopharmacology primarily focus on medication differences between those of Asian and European ancestries.<sup>1</sup> Most available studies are typically small and describe pharmacokinetic outcomes but not always clinical outcomes. In addition to the few studies comparing medication responses across diverse populations, it is also important to consider how psychiatric medications have made it to global markets. Historically, many psychiatric medication clinical trials have been conducted in North American or Western European countries, resulting in the enrollment of subjects of mostly European ancestry. While over the last decade, there have been implementations of policies, guidance, and even new 2023 legislation signed to improve diversity in clinical trials, many groups remain underrepresented, and these limitations should be recognized.<sup>8-10</sup> As the FDA does have guidance on the reporting of demographic information, the prescribing information (PI) for some medications does mention whether factors such as age, gender, or race have been assessed before FDA approval, although the ability to detect differences in clinical trials may be limited, and the clinical usefulness of this information may be uncertain. As an example, the carbamazepine PI mentions, “. . . the effects of race and gender on carbamazepine pharmacokinetics have not been systematically evaluated,”<sup>11</sup> whereas the PI for escitalopram states, “Analyses of the relationship between treatment outcome and age, gender, and race did not suggest any differential responsiveness on the basis of these patient characteristics.”<sup>12</sup> For clozapine, there is negligible information within the PI describing variation of dosing or outcomes across different populations. The 1988 study that led to the FDA approval of clozapine for treatment-resistant schizophrenia was comprised of 65% White subjects.<sup>13</sup> Black patients represented 23% of the sample, while groups described as “Hispanic,” “Oriental,” and “Other” accounted for only 10%, <1%, and 1% of the sample, respectively. The 2003 study leading to clozapine’s FDA-approved indication for reducing the risk of recurrent suicidal behavior in patients with schizophrenia

or schizoaffective disorder included 70.7% White subjects, 15.4% Black subjects, and 1.2% “Oriental” subjects. Since clozapine’s initial FDA approval, the dosing recommendations have not significantly changed, although several publications have called for updates to the PI to bring attention to potential dosing differences across various ancestry groups.<sup>14–17</sup>

A growing number of studies have found that patients of East Asian ancestry require lower doses of clozapine to obtain serum concentrations similar to those of patients of European ancestry.<sup>3,18,19</sup> A 2022 guideline with input from an international group of authors proposed multiple inpatient clozapine titration strategies with considerations for ancestry, sex, and the presence of metabolic inducers or inhibitors.<sup>14</sup> The most conservative dosing is for female patients of Asian ancestry or “original peoples of the Americas” with factors suspected to decrease metabolism (eg, CYP inhibitors, obesity, or inflammation). For these individuals, clozapine is recommended to be started at 6.25 mg, increasing to 25 mg by the end of the first week of exposure and reaching just 75 to 150 mg by the fourth week of exposure. Thus, the common titration practice of increasing clozapine by 25 mg daily may be too rapid and decrease early clozapine tolerability in patients of Asian ancestry. As an example, a patient who might achieve a clozapine concentration of 150 ng/mL while on only 50 mg of clozapine after 2 days of titration is likely not at risk of severe clozapine sequelae but easily may experience unsatisfactory side effects that would negatively impact treatment acceptance and the likelihood of continuing clozapine long term. This “too rapid” titration may also precipitate an inflammatory response. Highlighted in the international guideline is clozapine’s influence on proinflammatory states ranging from benign and transient (eg, isolated fever) to potentially fatal (eg, myocarditis). These inflammatory processes are more likely to occur early in titration and with rapid titration, especially in those with reduced metabolism, such as patients of Asian ancestry. The early detection of clozapine-induced inflammation is important since acute inflammation inhibits CYP isozymes, including CYP1A2, CYP2C19, and CYP3A4, further decreasing clozapine clearance. As such, the guideline proposes weekly CRP monitoring (and, where available, troponin monitoring) for at least the initial 4 weeks of clozapine exposure to guide appropriate titration.<sup>14</sup>

For patients of “African ancestry,” the international guideline suggests the need for higher clozapine doses to obtain a therapeutic concentration than for patients of Asian or European ancestry. This suggestion was extrapolated from one pharmacokinetic study involving olanzapine, although other subsequent publications supported this notion.<sup>18–21</sup> Three publications in early 2023 evaluated large pharmacokinetic databases accounting for ancestry and other demographic information. All of the publications supported the trend of the need for lower clozapine doses for patients of

Asian ancestry and higher doses for certain African populations.<sup>18,19,21</sup> As an example, one of these studies predicted that a 300-mg clozapine dose would be required for patients of sub-Saharan ancestry to reach a therapeutic value (defined as 350 ng/mL), vs 220 mg for patients of European ancestry and 112 mg for patients of East Asian ancestry.<sup>18</sup> Potentially worrisome is that those authors also reported that patients of sub-Saharan ancestry actually had doses of clozapine similar to those of patients of European ancestry and were approximately half as likely to reach a clozapine concentration of 350 ng/mL. Further research is needed to better understand if undifferentiated dosing strategies contribute to a lower chance of a successful clozapine trial and the racial prescribing disparities that have been described.<sup>22–24</sup> Select studies describing antipsychotic use among different populations are highlighted in Table 1.<sup>17–21,25–28</sup>

There are limitations to the recommendations within the international guideline given that they are based on limited studies and expert opinion. They likely overgeneralize large and diverse continental populations. Thus, when titrating clozapine, these recommendations should be considered while also using clinical judgment. Larger, well-designed clinical studies are needed to better assess aspects related to clozapine initiation and titration for patients of different genetic ancestry backgrounds. Yet despite these limitations, case 1 presents a real-world scenario in which the use of a “standard” titration may have been too rapid based on the patient’s ancestry, leading to the development of adverse drug reactions (ADRs). Specifically, the clozapine titration was based on standard recommendations in the FDA-approved PI. The available data suggest that this titration rate is more appropriate for a patient of European or Western Asian ancestry. At the time of clozapine discontinuation, the concentration-to-dose (C/D) ratio was 3.95, which is suggestive of metabolic inhibition.<sup>29</sup> Under normal conditions, typical C/D ratios have been described to be 0.6 to 1.2 for populations of European ancestry and 1.2 to 2.4 for East Asian populations.<sup>30</sup> It is plausible that a rapid titration could have directly influenced an inflammatory process within the lungs, increasing susceptibility to pneumonia, or that inflammation decreased clozapine metabolism, resulting in sialorrhea and altered mental status, which are risk factors for pneumonia.<sup>14,31</sup> Notably, a 2023 study completed in Japan (where the usual titration rate is already lower than that in the United States) highlights that decreasing the rate of clozapine titration significantly reduced the risk of inflammatory reactions, even when controlling for age, sex, body mass index, valproic acid use, and smoking.<sup>32</sup> In case 1, unfortunately, CRP monitoring before the medical transfer or earlier clozapine concentrations were not obtained. However, this case depicts how slower titration with early CRP and serum concentration monitoring could have played a role in preventing clozapine discontinuation, which should not be viewed as inconsequential given the benefits of clozapine on outcomes such as suicidality and mortality.<sup>33–35</sup>

**TABLE 1: Select studies comparing antipsychotic concentrations between populations<sup>a</sup>**

Drug Studied and Reference	Groups Defined	Methods/Intervention	Results	Limitations
Haloperidol <sup>25</sup>	Han Chinese compared to “American” patients with schizophrenia (described as 3 Black patients and 15 White patients)	0.4 mg/kg haloperidol administered and controlled for weight	Han Chinese patients had a 52% higher serum concentration	Diet did differ, smoking information was not available for Han Chinese patients; small (18 matched pairs) study
Haloperidol <sup>26</sup>	Healthy volunteers, nonsmokers described as 12 “Caucasian” ( <i>n</i> = 12), American-born Asian (Filipino [ <i>n</i> = 5], Chinese [ <i>n</i> = 3], Japanese [ <i>n</i> = 2], and Korean [ <i>n</i> = 1]), and foreign-born Asian (Filipino [ <i>n</i> = 5], Chinese [ <i>n</i> = 3], Korean [ <i>n</i> = 2], and Japanese [ <i>n</i> = 1])	Given 0.5 mg IM haloperidol and 1 mg PO on 2 different days separated by 2 weeks; serum concentrations and prolactin were obtained	Similar haloperidol concentrations and prolactin increases were seen between Asian groups but were significantly different from those of the “Caucasian” group; tolerability was similar between groups	Small sample, low dosing
Olanzapine <sup>20</sup>	Patients with Alzheimer’s disease and schizophrenia enrolled in the CATIE and CATIE-AD trials	Population pharmacokinetics of olanzapine and patient-specific covariates were evaluated as potential contributors to variability in drug exposure	Patients who identified themselves as Black or African American cleared olanzapine 26% faster than patients of other races	Retrospective review of TDM information
Clozapine <sup>27</sup>	Indian patients with schizophrenia	Clozapine TDM completed to calculate C/D ratios	The median C/D ratio was 2.5, nearly double the C/D ratio expected for “Caucasian” patients; the average dose to achieve a therapeutic concentration for male smokers (238 mg) and female nonsmokers (120 mg) was estimated to be 40% lower than for “Caucasian” patients	Comparison group based on data published in a separate study
Clozapine <sup>17</sup>	20 Asian patients from Singapore of different ancestries (13 Chinese, 4 Indians, and 3 Malays) and 20 Caucasian patients from Australia with schizophrenia	TDM study controlling for gender, body mass index, and cigarette, alcohol, and caffeine use	Plasma concentrations were similar between groups despite Asian patients receiving a mean clozapine dose of 176 mg/day and the Caucasian group receiving 433 mg/day ( <i>P</i> < .001); remission was not correlated with clozapine dose, plasma concentrations, duration of illness, ethnicity, or gender	Small sample size, heterogeneous “Asian” group
Clozapine <sup>28</sup>	Patients from Canada described as Caucasian ( <i>n</i> = 36), African American ( <i>n</i> = 2), South Indian ( <i>n</i> = 1), Vietnamese ( <i>n</i> = 2), and Korean ( <i>n</i> = 1) and patients from Singapore ( <i>n</i> = 45)	Retrospective chart review to assess clozapine dosing and concomitant medications	The mean clozapine dose for “Canadian” patients was 408 mg/day vs 169 mg/day for the Asian patients	Retrospective chart review, limited to 2 mental health facilities



**TABLE 1: Select studies comparing antipsychotic concentrations between populations<sup>a</sup> (continued)**

Drug Studied and Reference	Groups Defined	Methods/Intervention	Results	Limitations
Clozapine <sup>21</sup>	Grouped patients with clozapine TDM described as Afro-Caribbean, White, Asian, “mixed ethnicity,” or ethnicity not recorded	371 610 clozapine samples were assessed based on dose, sex, ethnicity, age, body weight, and smoking	Smoking and Afro-Caribbean ethnicity predicted higher dosing, while female sex and Asian ethnicity predicted lower dosing	Did not control for the timing of the test performed or some other potential clozapine-related interactions
Clozapine <sup>18</sup>	The study assessed patients of 5 ancestral biogeographical groups: European, sub-Saharan African, North African, Southwest Asian, and East Asian	16 068 clozapine assays of patients ( <i>n</i> = 4495) from the UK with genomic data and clozapine TDM values available	Compared to those of European ancestry, (1) patients with sub-Saharan African ancestry had increased clozapine metabolism and were less likely to achieve concentrations of >350 ng/mL, and (2) patients of East Asian or Southwest Asian ancestry had decreased clozapine metabolism	Use of large biogeographical areas for groupings; could not account for adherence, smoking, weight, and concomitant medications
Clozapine <sup>19</sup>	Grouped patients with clozapine TDM described as Afro-Caribbean, White, or Asian	17 787 clozapine assays of patients ( <i>n</i> = 5960) from the UK with genomic data and clozapine TDM values available; the study accounted for dosage form, date/time of last dose, date/time of sample, age, sex, weight, and major clozapine interactions	Compared to White patients, the predicted dose in the model was 10% higher in Afro-Caribbean patients and 14% lower in Asian patients	Could not account for all factors such as caffeine use, estrogen treatment, the presence of inflammation, or hepatic dysfunction; the authors excluded patients of “mixed ethnicity”

CATIE = Clinical Antipsychotic Trials of Intervention Effectiveness; CATIE-AD = Clinical Antipsychotic Trials of Intervention Effectiveness—Alzheimer’s Disease; C/D = concentration to dose; IM = intramuscular; PO = oral; TDM = therapeutic drug monitoring; UK = United Kingdom.

<sup>a</sup>The terminology used in the table aligns with the authors’ text.

## Case 2: Pharmacogenomics in Diverse Populations

A 33-year-old South Korean patient presented to an outpatient appointment for an assessment of ongoing symptoms associated with a diagnosis of major depressive disorder and generalized anxiety disorder. The patient reported ongoing residual depressive symptoms for the last 2 years, worsening over that time. Symptoms included low mood, poor sleep, decreased energy, feeling cognitively slowed, hopelessness, and disturbances in her eating pattern. The patient reported decreased interest in the activities that she once enjoyed and persistent worries about job performance. Past medication trials were not sustained primarily due to ADRs and included paroxetine, sertraline, citalopram, venlafaxine, duloxetine, bupropion, and vilazodone. Fluoxetine at 20 mg daily was currently prescribed, with partial benefit, but 40 mg daily resulted in gastrointestinal upset and teeth clenching. In addition to nonpharmacologic approaches, pharmacogenomic (PGx) testing was recommended by the psychiatrist, who

noted the patient’s South Korean ancestry. Notable findings included a CYP2C19 poor-metabolizer status, a CYP2D6 normal-metabolizer status, a CYP3A4 normal-metabolizer status, and positivity for the HLA\*A 31:01 allele.

## Unraveling the Genetic Tapestry of Precision Medicine

While the application of PGx in psychiatry is expanding, the selection of psychiatric medications is more often based on patient-specific factors such as comorbidities, family history, and patient preference. Yet despite shared decision-making and patient-centered approaches, medication selection may be viewed as trial and error. In the example of major depressive disorder (MDD), under usual care, remission rates with an antidepressant may be 50% at best.<sup>36,37</sup> However, with the use of PGx testing to inform medication selection, a growing number of studies and meta-analyses suggest that remission rates in MDD can be improved.<sup>38–42</sup> Studies have also shown that

interactions can be avoided and that side effects can be reduced.<sup>38,43,44</sup> Yet there is a lack of data supporting the use of routine PGx testing to guide the selection of other psychiatric medications such as antipsychotics, mood stabilizers, or benzodiazepines. Even though many treatment guidelines remain outdated, in more recent guidelines, either PGx testing is not routinely recommended or insufficient evidence is cited to prevent any recommendation.<sup>45–47</sup> As a further example, the American Academy of Child and Adolescent Psychiatry issued a 2022 policy statement recommending against the use of “pharmacogenetic testing to select psychotropic medications in children and adolescents.”<sup>48</sup> The 2020 American Psychiatric Association guidelines for the treatment of patients with schizophrenia draw attention to antipsychotic PIs that recommend dose adjustments in the setting of an already known PGx status. However, the applicability of PGx testing to guide medication selection is questioned, with this being an area where further research is needed.<sup>49</sup> Other various guidelines (eg, the Clinical Pharmacogenetics Implementation Consortium [CPIC] and the Dutch Pharmacogenetics Working Group [DPWG]) and the PIs of some psychiatric medications recommend dose adjustments based on specific, already known CYP phenotypes but do not necessarily recommend preemptive PGx testing.<sup>50</sup> CPIC guidelines are available for only a limited number of antidepressants, including tricyclic antidepressants, citalopram, escitalopram, paroxetine, sertraline, and venlafaxine.<sup>51–53</sup> Also, while PGx-based recommendations from the DPWG or found within PIs include more medications, information is often based on limited pharmacokinetic data or theoretical clinical considerations.<sup>54,55</sup> In general, a lack of evidence to widely support the use of PGx testing in psychiatry, conflicting data, study methodology, and cost are some known barriers. Knowledge gaps and readiness to interpret results may also pose deterrents from ordering PGx testing or lead to misinterpretations.<sup>56</sup>

The use of pharmacodynamic gene variation information in psychiatry (eg, HTR2A, SCL6A4, COMT, and dopamine D2 receptor polymorphisms) is even more limited and currently cannot be recommended to guide the selection or dosing of psychiatric medications.<sup>50</sup> The 2023 CPIC serotonin reuptake inhibitor guideline specifically mentions that recommendations based on HTR2A and SLC6A genotypes cannot be provided because “the evidence supporting an association is mixed and/or insufficient to support clinical validity and utility at this time.”<sup>57</sup> Some meta-analyses have reported significant associations between the 5HTTLPR long allele and improved effectiveness or decreased side effects compared to the 5HTTLPR short allele in patients of European ancestry. This may not be generalizable across other populations.<sup>57,58</sup> Overall, caution or appropriate patient education is needed when reviewing pharmacodynamic gene results from commercial PGx products as they may overstate or overgeneralize the clinical impact based on a very small body of evidence.<sup>59</sup> One important exception is related to testing genetically at-risk

populations (ie., patients of Asian ancestry) for the HLA\*B 15:02 allele before starting carbamazepine and oxcarbazepine due to the risk of Stevens-Johnson syndrome or toxic epidermal necrolysis. Data linking other structurally similar agents and hypersensitivity reactions lead to considering HLA\*B 15:02 allele testing before starting (fos)phenytoin although less so for eslicarbazepine acetate and lamotrigine.<sup>60,61</sup>

In case 2, the clinician recognized that patients of Asian ancestry have a higher incidence of the CYP2C19 poor-metabolism phenotype, and this ended up being true for the patient. Incidentally, the patient was found to be at a higher risk (positive for HLA-A\* 31:01) for carbamazepine-induced Stevens-Johnson syndrome, toxic epidermal necrolysis, a drug reaction with eosinophilia and systemic symptoms, and maculopapular exanthema.<sup>60</sup> Relevant to CYP2C19, CPIC guidelines would apply to dosing or drug selection for several antidepressants, clopidogrel, and proton pump inhibitors. Compared to the wild-type (ie, normal) CYP2C19\*1 allele, loss-of-function alleles (eg, CYP2C19\*2 and CYP2C19\*3) have been widely assessed in patients of Asian ancestry. The CYP2C19\*2 allele can be found commonly in those geographically from East Asia (28.6% to 31%), Southeast Asia (28.9%), and South Asia (29.8% to 34%) but in up to 38% of Indian Singaporean populations. These rates are higher than for those of European (12% to 15%) and African (15%) ancestries. The CYP2C19\*3 allele is not as common across Asian populations, reported in geographic populations from East Asia (6.7% to 8.8%) and Southeast Asia (4.1%). The frequency of the CYP2C19\*3 allele may be higher in populations from Japan (11%), and this allele is rare (<1%) in individuals of European ancestry.<sup>62</sup> Again, intergroup differences should be recognized, but the generalized incidence of results for the CYP2C19 poor-metabolizer status varies across individuals of Asian (13% to 23%), African (6%), and European (2% to 5%) ancestries.<sup>62,63</sup>

It could be argued that this patient did not need PGx testing, and a cautious approach to future antidepressant initiation and titration could be taken. Yet while more cautious approaches are reasonable, avoidance or specific dosing decisions should be based on known PGx data at the individual level and not the presumption of a CYP450 polymorphism based on patient-reported ancestry.<sup>64</sup> If there are no barriers (eg, cost), the patient is interested, and both the potential benefits and shortcomings of PGx testing are discussed, testing should be considered. There may also be benefits for a patient in understanding potential reasons why past medications were ineffective or produced ADRs. For this patient, who self-reported as being South Korean, the likelihood of having a CYP2C19 intermediate-metabolizer (IM) phenotype could be as high as 47%, or approximately a 13% potential to be a poor metabolizer. While the CYP2C19 IM phenotype alone would not be as actionable based on

available PGx guidelines, there is the potential that it may be applicable to other nonpsychiatric medications in the future, such as clopidogrel.<sup>65</sup> In this specific case, the patient was a poor metabolizer of CYP2C19, which could explain the history of poor tolerability of some previous medication trials.

### Case 3: Words Matter

A psychiatric pharmacy resident aimed to compare whether the cost and length of stay differed between the use of first- and second-generation antipsychotic short-acting intramuscular injections. Race categories included in the demographic table were Caucasian, African American, and Other.<sup>66</sup> There is no mention of how these categories were derived in the methods, and although the Results section referred to the demographic table, there was no further elaboration or comment about race within the Discussion section. Ethnicity was not included or commented upon.

### Race, Ethnicity, and Genetic Ancestry in Medical Writing, Research, and Outcomes

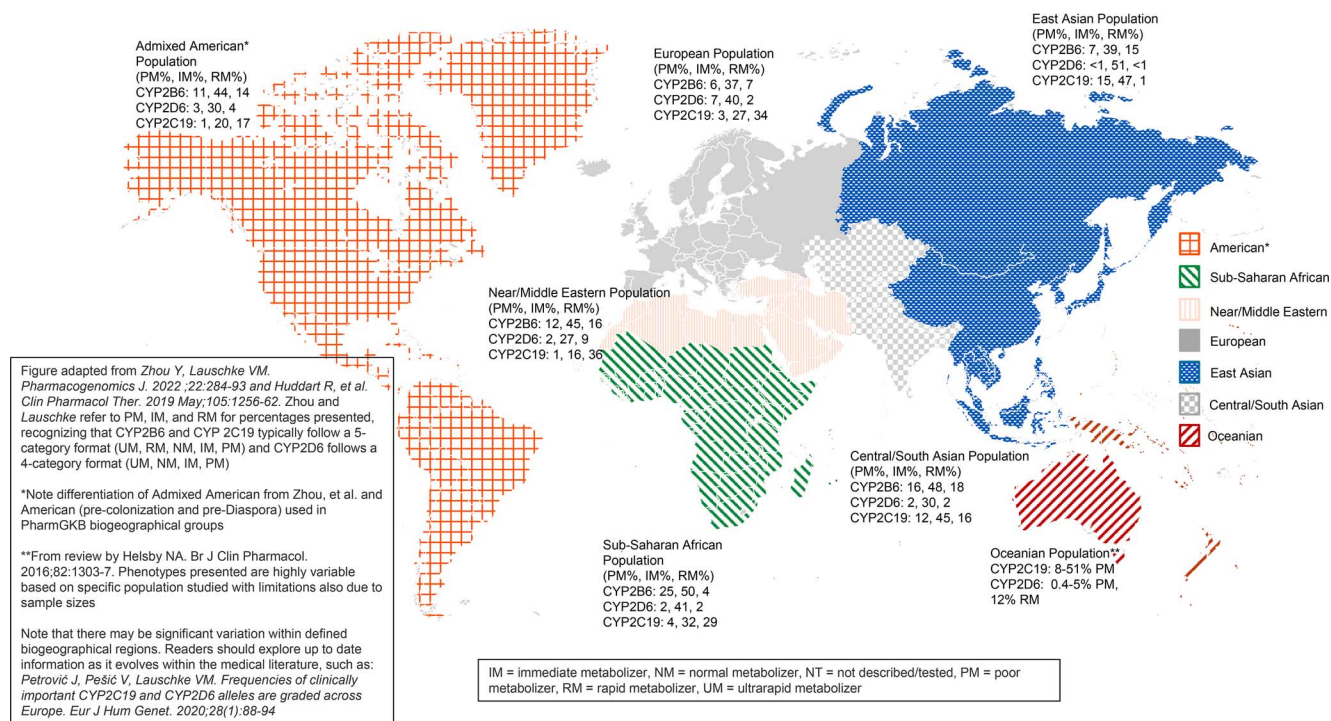
If the goals of ethnopsychopharmacology are to understand how medication outcomes are impacted by genetic, environmental, cultural, social, and historical factors, it is crucial to understand how the research methodology, reporting of data, and discussion of the results may influence the clinical application of information. Unfortunately, in the medical literature or in clinical practice, race and ethnicity can be used ambiguously or interchangeably. Even though there has been an evolution in the understanding and application of race and ethnicity, outdated or insensitive terminology is still encountered. Additionally, race and ethnicity, as social constructs, may be incorrectly applied as biologic surrogates of genetic predictions.<sup>67,68</sup> This is not to avoid the reporting and analyses of race and ethnicity as important factors or variables. Avoidance of the proper reporting of race and ethnicity can mask important findings related to health disparities and inequities involving social, cultural, or geographical factors.<sup>3</sup> Amutah et al summarized the above-mentioned findings by noting, “Granular ethnic categories that account for country of origin are better suited for discussions of genetic predisposition. However, these discussions should also encompass social context, to avoid reinforcing the inaccurate and harmful concept of distinct biologic races.”<sup>68</sup>

Problems in the literature are evident regarding how race and ethnicity are defined and how these data are collected and reported.<sup>69</sup> Data on race and ethnicity should be obtained based on direct reporting from patients or research participants. Limitations may exist when collecting these data retrospectively from an electronic health record due to inaccurate or missing data.<sup>70</sup> While there are no scientific definitions for race or ethnicity, the National

Institutes of Health (NIH) has guidance on reporting for purposes of government-funded research. Categories are based on the Office of Management and Budget (OMB) *Revisions to the Standards for the Classification of Federal Data on Race and Ethnicity*, which are also used for the US Census.<sup>71</sup> The OMB classifications have many limitations, and the OMB itself has cautioned that the use of categories “should not be interpreted as being scientific or anthropological.”<sup>72</sup> The current OMB race categories are (1) American Indian or Alaska Native, (2) Asian, (3) Black or African American, (4) Native Hawaiian or Other Pacific Islander, and (5) White. The OMB standards include one ethnic category, Hispanic or Latino. In the United States, race and ethnicity should remain connected, and the National Academy of Medicine recommends that combined race and ethnicity categories be used over race alone.<sup>68</sup> The National Academy of Medicine also recommends that granular ethnicity or ancestry (eg, country of origin) should be used when describing a genetic relationship between individuals or groups and results.<sup>68</sup> Also, in the literature, there may be divergence in how racial and ethnic categories are defined and used between countries. Many countries do not recognize race as a category. As an example, countries of the United Kingdom do not define racial categories for census purposes but rather solely “high-level” ethnicity groups, in which individuals may specify identifying with a more specific group via a write-in option. Because of this, it has been recommended to avoid applying OMB categories to research subjects of studies conducted outside the United States (eg, when pooling data for a meta-analysis).

To better reference biological populations or describe differences among groups, a system involving biogeographical groups is being used in pharmacogenomic research. The nomenclature was created to standardize biologic constructs within research as opposed to social ones and capture genetic patterns. This system involving multiple population genetic data sources is used by the Pharmacogenomic Knowledgebase (PharmGKB).<sup>73,74</sup> PharmGKB is funded by the NIH and contains extensive information from research sources regarding the genetic variations in drug responses that are summarized for clinicians and researchers. In 2018, PharmGKB phased out the use of OMB categories to favor the use of a system comprised of seven biogeographical groups: American, Central/South Asian, East Asian, European, Near Eastern, Oceanian, and sub-Saharan African. The categorizations are based on populations from global regions with “common genetic ancestry pre-colonization and pre-Diaspora.”<sup>74</sup> Two additional groups include African American/Afro-Caribbean and Latino populations, which are described as “populations with a significant degree of post-colonization and post-Diaspora gene flow between distinct geographical populations.” Complete definitions as well as origins of biogeographical groups can be found on the PharmGKB website.<sup>73</sup> Discussion related to the origins of modern human ancestry can be found





**FIGURE: Representation of pharmacogenomic knowledgebase biogeographical groups and examples of reported global cytochrome P450 phenotypes**

elsewhere.<sup>75,76</sup> Recognizing that there is significant variation within these more broadly defined populations, the Figure, with limitations, depicts the biogeographical groups, precolonization and pre-Diaspora, adopted by PharmGKB and variations in metabolizer status across different groups based on several reports.<sup>64,77,78</sup> Variation within specific biogeographical groups has been described, although the majority of the literature has studied populations from the Americas, Europe, and Asia.<sup>62,79,80</sup> More recently, there have been several major initiatives to improve pharmacogenomic understanding and knowledge for patients of African ancestry, such as the African Pharmacogenomics Consortium and the African American Cardiovascular Pharmacogenetic Consortium.<sup>81,82</sup>

In addition to OMB standardized language, there is further guidance on the reporting of race and ethnicity from sources such as the *AMA Manual of Style* or the International Committee of Medical Journal Editors standard requirements.<sup>83,84</sup> The guidance aims to reduce unintentional bias and includes recommendations such as (1) defining the race and ethnicity variables used, (2) reporting who classified the variables, (3) indicating the method used to investigate the variables, and (4) whether terms were classified based on the investigator or participant. It is also recommended to provide why race and ethnicity are addressed and if they were an integral part of the study design, setup, and research question.<sup>69,85-87</sup> Authors should have clarity and intent when planning research, analyzing data, and writing manuscripts that include data on race or ethnicity, even if limited to descriptive information on

demographics. The purpose of the inclusion of all data, the method of collection, and the implications of relevant findings should be clear to the readers evaluating the literature. Despite guidance, the conscientious use of race and ethnic categories in the literature has been described as lacking rigor or precision and can be found to be inconsistent among studies.<sup>88</sup> Ensuring the use of only one term to describe a single population throughout a manuscript is also important for clarity. Publications can be found that inappropriately refer to a single described population with several terms interchangeably, such as using White and Caucasian or Black and African American. Furthermore, the use of Caucasian is imprecise unless referring to individuals from the Caucasus region, not analogous to the commonly associated race category, White.<sup>89,90</sup> Calls to avoid the term Caucasian have been amplified by several well-known journals, the NIH, and the 2021 *AMA Manual of Style* update.<sup>3</sup> Unfortunately, the term Caucasian continues to be found commonly in the medical literature, even in 2023.<sup>3,68</sup>

It is also important to remove biases from patient care by examining currently used medical terminology and updating it to be accurate based on known scientific data. This was recently addressed with vancomycin infusion reactions, often previously (and likely still) referred to as “red man syndrome,” and recommendations to remove race in the Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) equation for estimating glomerular filtration rates.<sup>91-95</sup> In the field of hematology, and relevant to



**TABLE 2: Select recommendations on the reporting of race and ethnicity in the medical literature<sup>a</sup>**

**Examples from the AMA Manual of Style: A Guide for Authors and Editors<sup>93</sup>**

- The purpose for the collection and assessment of race and ethnicity categories should be outlined in the Methods section. The study Methods section should detail who identified participant race and ethnicity and the source used (eg, the patient reported to the electronic health record).
- Categories should be alphabetized in the text and tables. The use of an “Other” category for convenience should be avoided. If needed for analysis due to a small sample size or if a prior database previously defined and used this term, this should be clarified and reported.
- Avoid the term *Caucasian*, which refers to people from the Caucasus region of Eurasia.
- Do not hyphenate terms such as *Asian American* and *African American*.
- Refer to “race and ethnicity” over “race/ethnicity.” Use the adjectival form for racial and ethnic terms (eg, Asian patients) and not nouns (eg, Asians).
- The use of “multiracial” and “multiethnic” is acceptable when predefined or self-selected. There is a recommendation to report the sample of individuals reporting more than one race. “Mixed race” should be avoided.
- The combining of racial and ethnic minority groups as “non-White” should be avoided. Avoid “non-” terms in general.
- Capitalization should be used for the names of races, ethnicities, and tribes.

**Examples from the NIH Style Guide<sup>100</sup>**

- An Alaska Native (not Alaskan Native, which denotes a resident of Alaska) is a person whose origins are from any of the original peoples of Alaska and who maintains cultural identification through Tribal affiliation or community attachment.
- Do not use the word *Oriental*.
- Only use Latinx if someone has said they identify that way; it is not accepted by many.
- *Hawaiian* refers to individuals of Polynesian descent and is not specific to everyone living in Hawaii.
- The terms Black and African American are not synonymous. The NIH provides the example that an individual “could be born in Jamaica and live in the U.S. and identify as Black but not African American.”

<sup>a</sup>Readers are suggested to read the freely available *AMA Manual of Style* chapter for detailed explanations and examples. The guidance “acknowledges that these terms and definitions have changed, that some are out of date, and that the nomenclature will continue to evolve.” Additional information may be found using the *NIH Style Guide* at <https://www.nih.gov.nih-style-guide/race-national-origin>. The framework has limitations, and where possible, categorization should be as specific as possible and avoid overgeneralizations, which can have negative consequences.

psychiatry, there is a call to avoid the use of what has been referred to as benign ethnic neutropenia (BEN). This manifests as chronically low but nonpathologic absolute neutrophil count (ANC) values, occurs primarily in individuals of African ancestry but also those of Middle Eastern ancestry, and is genetically associated with rs2814778, a single nucleotide polymorphism found at the promoter region of the ACKR1 gene (previously known as the Duffy antigen receptor for chemokines gene). The term BEN has fallen out of favor for either “Duffy-null-associated neutrophil count” (DANC) or “typical neutrophil count with Fy(a<sup>-</sup>b<sup>-</sup>) status.”<sup>96,97</sup> This is because neutropenia implies pathology or abnormality (when none exists for DANC), relative to what is deemed “normal” neutrophil counts for other patients. In an editorial published in *Blood*, the journal of the American Society of Hematology, Merz et al called for the adoption of Duffy-null reference ranges for neutrophil counts.<sup>97</sup> Survey data suggest that hematologists favor the change in language, which should be adopted in psychiatry as well.<sup>98</sup> Additionally, research supports that the presence of the Fy(a<sup>-</sup>b<sup>-</sup>) phenotype is the best diagnostic method for the determination of “BEN,” with greater sensitivity and specificity than the use of self-identified race or ethnicity.<sup>96</sup> The understanding of DANC has been important in psychiatry as it relates to clozapine initiation and ANC monitoring in patients with nonpathologic but chronically low ANC values. Following the 2015 creation of two FDA-approved monitoring pathways (ie, general population and “BEN” population), patients with DANC

faced fewer barriers prohibiting clozapine initiation and continuation.<sup>99</sup> Currently, the Clozapine Risk Evaluation and Mitigation Strategy program still refers to “BEN.”

While what is considered appropriate, nonbiased language for use in scientific literature continues to evolve, some standardized approaches exist and can apply to primary investigators of a study, mentors of residency research projects, peer reviewers, journal editors, and even those assessing medical literature. As in case 3, and like in many other publications, there are race and ethnicity data presented that are incomplete, mischaracterized, or lacking explanation. Studies should describe the method by which race or ethnicity data are obtained and recorded, even if for retrospective studies, which might specify that information was extracted from a medical record or, where possible, indicate whether the information originated by patient self-report. When study staff can electronically gather patient-specific demographic information, those involved should understand where the information came from and how it originated so that it can be described in a study’s methods. Those assessing medical literature should be mindful of this as well. Second, the authors of case 3 refer to the category “Caucasian,” which is likely not the intended term and should not be used if meaning the OMB race category White. Third, in case 3, it is not known whether the use of African American is accurate or imprecise, as it may not be analogous to the OMB category of “Black or African

American” or representative of a patient’s self-identity. A clearer description of how data on race were originally gathered and then collected would have mitigated this issue. Finally, an “Other” category is described in the case 3 publication. The use of “Other” as well as the use of “non-” terms (eg, non-White) are discouraged but can be found in as many as 30% of published papers.<sup>69,100</sup> Additional examples of important guidance from *AMA Manual of Style* and *NIH Style Guide* considerations for authors of medical literature are highlighted in Table 2.<sup>93,100</sup> Of note, the *AMA Manual of Style* also includes guidance that addresses the use of verbiage related to (1) sex and gender, (2) sexual orientation, (3) personal pronouns, (4) age, (5) socioeconomic status, and (6) diseases, disabilities, and disorders.<sup>93</sup>

## Conclusion

While ethnopsychopharmacology explains medication responses based on biologic and nonbiologic factors, there are significant complexities in being able to research both aspects within a study large enough to be meaningful. In certain cases, drug dosing may be guided based on knowledge of a patient’s ancestry, as in the case of clozapine. Additionally, awareness of CYP polymorphism trends across patients of different ancestries may be helpful when pharmacogenomic testing is not completed or available. Research is needed to better account for both biologic and nonbiologic factors to truly describe ethnopsychopharmacology outcomes. How patient-specific factors are evaluated (or not) and reported in the literature may influence data interpretation, the applicability of results, and patient outcomes. The cognizant use and understanding of up-to-date inclusive language are important for all in health care.

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