Pharmacotherapy

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Introduction

The Centers for Disease Control and Prevention has reported that 6–7.5 % of children between 6 and 19 years of age are prescribed medication for behavioral or emotional difficulties (Howie, Pastor, & Lukacs, 2014; Jonas, Gu, & Albertorio-Diaz, 2013). There is a disparity of mental health service utilization by minority youth especially among African Americans. Cuffe, Waller, Cuccaro, Pumariega, and Garrison (1995) observed that African American girls received treatment a third less and African American boys at half the rate of non-Hispanic white boys. Zito, Safer, dos Reis, and Riddle (1998) reported African American and Latino youths have a reduced likelihood of being prescribed psychotropic medications compared to non-Hispanic white youth. While two older studies found no disparities between different ethnicities (Burns et al., 1995; Costello & Janiszewski, 1990), recent work has reported that depressed African American adolescents are about half as likely when compared to their white counterparts to receive antidepressant treatment (Wu et al., 2001).

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Of the 6.3 % of adolescents who are prescribed psychotropic medications, 4.5 % take one medication and 1.8 % take two or more medications (Jonas et al., 2013). About 3.1 % of non-Hispanic black adolescents take medications, compared to 8.2 % of non-Hispanic white adolescents. Overall, 3.2 % take antidepressants, 3.2 % take stimulant medications, 1 % receive antipsychotics, 0.5 % anxiolytics, sedatives, or hypnotics, and 0.2 % take antimanic agents. While girls are more likely to be prescribed psychotropic agents in general, boys are more likely to be on medications to manage attention deficit hyperactivity disorder (ADHD) symptoms. Children below 100 % of the poverty level or those insured by Medicaid or Children's Health Insurance Program (CHIP) are more likely to receive drugs for emotional or behavioral difficulties (Howie et al., 2014). The use of psychotropic medication is lower in non-Hispanic black (3.1 %) and Mexican–Americans (2.9 %) than non-Hispanic white adolescents (Jonas et al., 2013).

A review of the literature regarding psychopharmacology in African–American youth supports the need for continued research in this growing population of patients. The lack of significant historical psychopharmacologic research exploring potential differences between blacks, whites, and other racial groups in the USA makes this a difficult area of clinical study (Miskimen, Marin, & Escobar, 2003). Very low rates of participation by ethnic minorities in studies result in an inability to assess

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intra- or interracial efficacy of medication within these groups or in comparison with majority populations, respectively (U.S. Department of Health and Human Services, 2001). As a result, the National Institutes of Health (NIH) Revitalization Act of 1993 mandated that minority group enrollment in clinical trials be of sufficient statistical power to ensure that significant differences in results related to race or ethnicity could be detected (Freedman et al., 1995; US Congress. NIH-Revitalization-Act, 1993). Despite this, there remains a paucity of data that evaluates psychotropic medications in the pediatric African–American population.

Pharmacotherapeutic Perspectives

There are several aspects of pharmacotherapy that can be explored from basic science and clinical research to help identify and explain potential ethnic variability in clinical responses to treatment. An individual's pharmacologic response, metabolism, and elimination of psychotropic drugs are based on genetically determined physiologic systems. The practice of psychopharmacotherapy combines prescribing and psychotherapy skills (Pruett & Martin, 2003). This requires attending to the therapeutic relationship, the patient's affect, attitudes, behavior, and thoughts as well as the social and developmental contexts of the prescriber–patient relationship.

The majority of studies have focused on Caucasian and Asian ethnicities with limited focus on African American and Hispanic populations. Hypotheses for differences in ethnic/race response include pharmacokinetic and pharmacodynamic variations, and non-pharmacological explanations, such as cultural and societal variations in the way psychiatry is practiced (Frackiewicz, Sramek, Herrera, Kurtz, & Cutler, 1997). Pharmacokinetic and pharmacodynamic responses are better explained through pharmacogenomic processes. Pharmacokinetics is the study of how the body absorbs, distributes, metabolizes, and eliminates medications. Pharmacodynamics focuses on how medications affect the body, including, but not limited to, therapeutic and adverse effects. Pharmacogenomics explores the relationship of both of these processes and genetic differences that may relate to ethnic differences and efficacy.

It is challenging to examine the effects of cultural variability on efficacy and adverse effects of psychotropic medications because race and ethnicity are not measurable or defined consistently. Studies from purely biologic perspectives "may undercut research into variability that would be captured by cultural variables" (Stewart, Simmons, & Habibpour, 2012, p. 75). Because there is no acceptable gold standard as to whom or how to assign a participant to the categorical dimensions of race or ethnicity, one can argue that ethnic-based research is less empirical.

Between 1975 and 2014, the evaluation of ethnic differences and response to medications has been increasing, but remains limited with regard to children of diverse populations. The lack of direct evidence makes it necessary to extract and merge information from pediatric and adult African American literature to speculate on the existence of pharmacologic variability among pediatric African American populations. We will explore information specific to African Americans and youth separately. Limited information specific to African American youth will be provided when available.

Clinical Variations in African American Adults

Antidepressants

The evidence comparing depression treatment outcomes by ethnicity has had mixed results. Some studies show poorer outcomes for minority patients than Caucasians while others suggest a more rapid response in treatment for African Americans and Latinos when older antidepressants are used. Varner, Ruiz, and Small (1998) provided evidence suggesting that blacks need lower doses of tricyclic antidepressants (TCAs) and SSRIs than white patients to attain a similar response in the treatment of major depression. Two other studies have described similar results that black patients achieve higher TCA concentrations in the blood and have a faster rate of recovery

when treated with either amitriptyline or imipramine (Raskin & Crook, 1975; Ziegler & Briggs, 1977).

A subanalysis of the Sequenced Treatment Alternatives to Relieve Depression (Star*D) Study adjusted for baseline differences in insurance, severity of depression, comorbidities and level of impairment revealed that African Americans had less response to antidepressants. They speculated that continued research is needed to identify the variables (socio-demographic, versus economic, versus biologic versus other) with the most impact on treatment outcomes (Lesser et al., 2005, 2007).

Antipsychotics

The literature is scarce investigating whether or not different racial or ethnic backgrounds affect a patient's response to antipsychotic treatment. Again, the results and conclusions are mixed. Ruiz, Varner, Small, and Johnson (1999) studied the response to neuroleptics for schizophrenia in white, black, and Hispanic patients. Hispanic patients required the lowest dosing for effective treatment. When weight was taken into consideration, the dosing between the white and black patients was no different. However, a South African study compared baseline Positive and Negative Syndrome Scale (PANSS) scores following atypical and conventional antipsychotics in various ethnic groups. Emsley et al. (2002) found that baseline scores were higher for black and mixed heritage patients compared to whites. They also found a greater reduction in scores following treatment among these groups compared to whites. Furthermore, they speculated that delayed treatment may have contributed to high baseline scores for black and mixed heritage individuals.

In any discussion of potential racial disparities of pharmacologic effects of psychotropic drugs, side effects and adverse reactions must also be explored (see Table 3.1). Ormerod, McDowell, Coleman, and Ferner (2008) reported that ethnicity reflects components of both genetic and exogenous variability that are known to influence susceptibility to adverse drug reactions (ADRs). Ethnic differences in side effects may stem from genetic differences in pharmacokinetics or pharmacodynamic factors.

African American patients are more likely to be diagnosed with schizophrenia than white patients, more likely to receive higher doses of treatment, and less likely to receive newer classes of antipsychotics (Lehman et al., 1998; Mukherjee, Shukla, Woodle, Rosen, & Olarte, 1983). African American patients receiving first generation antipsychotics (FGAs) appear to be at greater risk for movement disorders such as tardive dyskinesia (TD; Morgenstern & Glazer, 1993).

While FGAs were found to be effective for treating psychosis, there were multiple untoward effects, such as extrapyramidal symptoms (EPS) and TD (Geddes, Freemantle, Harrison, & Bebbington, 2000). These types of movement effects may impact a patient's adherence to treatment. African American patients are less likely than white patients to receive second-generation atypical antipsychotic medications (SGAs) (49 versus 66 %, respectively). They tend to be prescribed agents that are not the currently recommended first line drugs (Mark, Dirani, Slade, & Russo, 2002; Wang, West, Tanielian, & Pincus, 2000). They receive medications that have greater risks of producing EPS and TD. The same studies reported that younger male African Americans with schizophrenia were less likely to receive SGAs than their white counterparts. However, when controlled for Medicaid enrollees or for socioeconomic status, the study did not reveal a racial disparity in the use of SGAs. This observation is consistent with the conclusion that access to quality care or payer mix may also be predictors of outcome independent of race and ethnicity.

The relationship between ethnicity and susceptibility to ADRs may be influenced also by differences in the way adverse effects are described by patients of different ethnicities. Several studies reported an increased risk of TD in certain ethnic groups, particularly black patients. This observation may be a reflection of choice of medication more than ethnic variability per se.

Lawson, Herman, Loebel, Lazariciu, and Malik (2009) noted that the use of SGAs instead of FGAs in African Americans should result in a lower risk for extrapyramidal side effects. In a study by Binder and Levy (1981), there was no statistically significant difference in the development of EPS

Table 3.1 Potential racial disparities of pharmacologic effects of psychotropic drugs, side effects, and adverse reactions

Adverse effect	Potential ethnic variation	Strength of evidence
Tardive Dyskinesia	Risk greater in blacks versus whites with use of antipsychotics	Difference observed in cross-sectional study (Morgenstern, Glazer, Gibowski, & Holmberg, 1987); No difference in prevalence in cross-sectional or prospective trials (Chakos et al., 1996; Jeste et al., 1995; Morgenstern & Glazer, 1993; Oosthuizen, Emsley, Maritz, Turner, & Keyter, 2003; Van Os et al., 2000)
Hyperglycemia	Complication greater in blacks versus whites with use of atypical antipsychotics	Occurrence in 19 versus 10 %, black versus white, respectively—not significant; (Lindenmayer et al., 2003) Two cross-sectional trials show no difference (Sernyak, Gulanski, Leslie, & Rosenheck, 2003; Sernyak, Gulanski, & Rosenheck, 2005)
Diabetes mellitus	Antipsychotic complication greater in blacks and Hispanics versus whites	Odds ratio over 10-year naturalistic study black versus white 11.5, Hispanics versus white 4.3 (Henderson et al., 2005). Clozapine nonwhite increased risk observed (Barner, Worchel, & Yang, 2004)
Cardiovascular mortality	Antipsychotic complication increased in black/Hispanic versus white	Noted in one study (Henderson et al., 2005)
Metabolic Syndrome	Prevalence white versus nonwhite	None observed in one study of second generation antipsychotics except hypertriglyceridemia was more common in whites (Correll, Frederickson, Kane, & Manu, 2006)
Weight gain	More rapid weight gain nonwhite versus white for some agents but not all	Randomized masked trial olanzapine versus haloperidol; olanzapine versus risperidone (Basson et al., 2001; Zipursky et al., 2005)
Blood disorders	Neutropenia greater risk, black versus white	Risk 77 % greater black versus white for clozapine (Munro et al., 1999)

Based on Ormerod et al. (2008)

in African Americans and Caucasians after two weeks of treatment with haloperidol.

When it comes to TD, the available evidence is conflicting. In a study by Glazer, Morgenstern, and Doucette (1994), non-Caucasians were 1.83 times more likely to develop TD compared to Caucasians; however, this study only included three African American patients and assessed new occurrence of TD in patients treated with schizophrenia. In a study by Sramek et al. (1991), there was no statistically significant difference between African Americans and Caucasians in the prevalence of TD in patients hospitalized for greater than one year.

However, in a meta-analysis designed to review the evidence of potential ethnic differences in adverse reaction susceptibility to antipsychotic and antidepressant medications, the results regarding blacks, East Asians, and South Asians were inconclusive. The only significant result was the relative risk for EPS being higher among East Asian versus non-East Asian patients (1.38, 95 %, CI 1.11–1.72) (Ormerod et al., 2008). They too speculated that there is a need for further research into the genetics of ADRs. Furthermore, they noted the need for transparency in ethnic group nomenclature in order to design clinically relevant multi-ethnic studies.

Bipolar Treatment and Other Considerations

Strickland, Lin, Fu, Anderson, and Zheng (1995) reported that African Americans show a higher red blood cell (RBC) plasma ratio of lithium

concentration when compared with Asians and whites. Malik, Lake, Lawson, and Joshi (2010) presumed this higher lithium concentration was due to the tendency of African Americans to retain sodium. They noted that some believe sodium retention offered a selective survival advantage for slaves brought to America over the Middle Passage because hyponatremia was believed to be the major cause of mortality. Strickland et al. (1995) reported more side effects in African American patients with high RBC/plasma ratio even when the lithium levels were in therapeutic range. Whether African Americans require lower doses of lithium or respond at lower lithium plasma levels remains an open question.

Irrespective of the observations noted here with regard to antidepressant or antipsychotic medication ethnic response variability, there are data from a study by Lesser et al. (2010) that suggest access to and quality of psychiatric care in general may be the most relevant determinants of outcome disparities regardless of diagnosis. Ethnicity, younger age, and socioeconomic disadvantage have been identified as risk indicators for poor treatment outcomes and premature discontinuation of treatment (Harman, Edlund, & Fortney, 2004; Virnig et al., 2004; Wagner, Maguen, & Rabkin, 1998).

Research on efficacy and side effects with sizable numbers of ethnic minority participants is still quite limited. There is as much heterogeneity within an ethnic or racial group as there is between groups. This makes research in ethnic minority populations in the USA difficult. The lack of consistent findings emphasizes the importance of including both adult and pediatric racial and ethnic minorities in clinical trials in sufficient numbers to draw inferences regarding race and ethnicity. Failing to do so leaves minorities at potentially increased risk for idiosyncratic side effects, or ineffective or toxic dosing. Until this is done, evidence-based treatment guidelines will not be able to be developed to enhance the psychopharmacologic treatment of African–American youth. This coupled with genetic variability in psychopharmacologic response to psychotropic drugs may play a role in adherence to treatment decisions made by patients, parents, and clinicians.

Psychopharmacology in African American Youth

It is reasonable to presume that the apparent disparities in psychiatric diagnosis, treatment and psychopharmacologic variability between ethnic minority and white children would mirror those reported in adults. The limited availability of information is even more pronounced in pediatric than in adult medicine. Currently, utilization of available mental health services and unmet needs are a primary focus of child and adolescent psychiatric clinical research.

Information detailing differences between white and minority youth regarding pharmacodynamics and pharmacokinetics of antidepressants is limited. As of 2012, there were no published randomized controlled trials investigating ethnic differences in pharmacotherapy of pediatric depression.

The literature has been inconclusive regarding metabolism of pharmacological agents or doses at which antidepressant efficacy or adverse reactions become apparent in the treatment of ethnic minority youth. African American adults have a lower tolerance for some antidepressant medications. It may be reasonable to extrapolate these results to African American youth when dosing decisions are made by clinicians.

Use of antipsychotics in African American youth has been scarcely studied. In one study, Wonodi et al. (2007) found that 9 of 62 African American children (15 %) on antipsychotic medications exhibited TD compared with only 4 % (2 of 52) white children. This study was one of the first reports describing the vulnerability of children to TD following exposure to SGAs only. In 2007, SGAs were thought to be associated with significantly reduced risks of TD in chronically treated adult and pediatric patients. Wonodi et al. suggested that the untoward effects of both FGAs and SGAs might be more prevalent and severe in children than that described in adults. Two studies indicated that co-administration of conventional antipsychotics and stimulants may potentiate a movement disorder in children (Casat & Wilson, 1986; Gualtieri & Patterson, 1986).

Attention Deficit Hyperactivity Disorder

ADHD is the most studied condition in pediatric pharmacogenetics. The finding that African Americans were treated 2/3 as often as whites for ADHD may be secondary to parental beliefs about ADHD, higher rates of risk, lack of treatment access, or non-adherence to prescribed medications. When African American children take stimulants, there may be significant differences in treatment response compared with white children. Some observational studies have described a greater nonresponse to stimulants in African American children. However, these studies had no comparison groups, included a small number of subjects, or the results were not significant (Arnold et al., 2003; Winsberg & Comings, 1999).

There are a few studies evaluating the tolerability of ADHD medication in children. Again, these studies are small but do demonstrate trends towards greater adverse effects from ADHD medications in African American children. For example, Brown and Sexson (1988) found methylphenidate improved attention and impulsivity with a linear dose effect. However, there was a trend towards an increase in side effects with increasing doses, including an increase in mean diastolic blood pressure.

Starr and Kemner (2005) performed a subgroup analysis on the African American participants in the Formal Observation of Concerta versus Strattera (FOCUS) study. They found that both methylphenidate and atomoxetine provided improvement in baseline symptoms, with similar incidences of adverse events in African American children. They concluded that there was no ethnic difference in tolerability of methyphenidate-oros (osmotic release oral system) and atomoxetine; however, this study was of low power.

Pharmacologic Variability

Recent studies are beginning to consider genes, neurotransmitters, and transport systems as explanations for the variability in response to treatment and ADRs. Hypotheses for the variations in ethnic/race response include differences in pharmacokinetics, pharmacodynamics, and non-pharmacological explanations such as cultural and societal variations in the way psychiatry is practiced (Frackiewicz et al., 1997). The pharmacokinetic and pharmacodynamic responses are better explained through pharmacogenomic processes.

Pharmacokinetics is the study of how the body absorbs, distributes, metabolizes, and eliminates medications. Pharmacodynamics focuses on how the medications affect the body, including, but not limited to, therapeutic and adverse effects. Pharmacogenomics explores the relationship of both of these pharmacologic processes and genetic differences that may relate to ethnic differences and efficacy of response.

Pharmacogenomics

Pharmacogenomics can provide insight into the most appropriate medication choice in treatment-resistant individuals and those at increased risk of developing adverse effects. Pharmacogenomics can be divided into two basic categories: (1) metabolic enzymes effecting pharmacokinetic parameters and (2) genes that effect neuronal function or pharmacodynamic parameters. Examples of genes affecting pharmacokinetics include those that code for Cytochrome P450 (CYP450) enzyme systems, while those affecting pharmacodynamics include catecho-O-methyl transferase (COMT) and dopamine receptors 2 and 4 (DRD2, DRD4).

The science of pharmacogenomics relates to a variety of mechanisms of polymorphism. Polymorphisms are naturally occurring genetic variations within a population. These interactions may be complex, such as when various genetic contributions alter the pathology of a disease state to simple effects related to drug availability. Polymorphisms occur by four different mechanisms: (1) pharmacokinetic gene variation influences drug disposition and availability, (2) variation in the effect on target gene mediation of clinical response, (3) genetic influences on a drug's initial mechanism of action resulting in an indirect

modification of its response, and (4) genetic alterations that affect disease pathology (Reynolds, 2007).

Variable strength of cytochrome P450 (CYP450) 2D6 drug metabolism is an example of a metabolic polymorphism. For atypical antipsychotics such as clozapine, altered binding at the serotonin (5-HT)2A receptor gene is an example of a drug mechanism polymorphic pathway. Other examples include studies that suggest inter-individual genetic variation within a population related to drug-induced weight gain (Reynolds, 2007).

Pharmacokinetic Variability in Adults

The study of pharmacogenomics is governed by the principle of genetic polymorphisms. The majority of the available clinical evidence centers on adult patients. A small amount of literature reviews the effects of polymorphisms on adult African Americans with an even smaller amount of information available for children. Speculation must be inferred from adult studies until further research addresses these issues in this unique population.

Polymorphisms of drug metabolic mechanisms have received the most attention in pharmacogenetic research because of their clinical relevance and impact a large number of patients who take psychotropic medication.

Cytochrome P450 Cytochrome P450 (CYP450) enzymes are a huge focal point of study when determining medication responsiveness versus the toxicities of these agents. Polymorphic CYP450 enzymes are the largest class of drug-metabolizing enzymes (see Table 3.2). The most notable are CYP1A2, 2B6, 2C9, 2C19, 2D6, 3A4, and 3A5 (see Tables 3.2 and 3.3). The majority of variability is related to single nucleotide polymorphisms (SNPs) expressed as variations in CYP450 activity. Each SNP represents a single variation in the DNA sequence. SNPs are normal variations and occur frequently throughout the sequence. Most SNPs have no effect on a person's health or development. However, some SNPs have evolved within specific ethnic populations that may explain therapeutic responses to lower doses or higher risk for adverse effects of medications within certain ethnic groups. Compared to Caucasians, African Americans and Asians exhibit lower CYP1A2 activity. Lower enzymatic activity means that the elimination of the medication is decreased with higher than expected amounts of the medication in the body. This may increase the risks of adverse effects and toxicity. For example, the elimination of clozapine and olanzapine is highly influenced by the activity of CYP1A2 (Murray, 2006). CYP2D6 and 3A4 may also influence elimination of these antipsychotics.

Table 3.2 CYP450 examples

CYP450 enzyme	Percentage of drugs metabolized	Examples of major substrates
1A2	10 %	Clozapine, haloperidol, olanzapine, thioridazine, trazodone
2C8/9/19	25 %	2C9: amitriptyline, fluoxetine 2C19: amitriptyline, citalopram
2D6	16 %	Aripiprazole, haloperidol, perphenazine, risperidone, and thioridazine, most tricyclic antidepressants
2E1	4 %	Acetaminophen, ethanol
3A4/5	34 %	Quetiapine, risperidone, ziprasidone
Others	11 %	2B6: bupropion

While CYP2C8/9/19 metabolize about 25 % of available medications, they represent 20 % of the liver CYP450 enzymes (McGraw & Waller, 2012). Of the group, CYP2C9 displays the highest level of expression over CYP2C8 and CYP2C19. Within each CYP450 enzyme group, there are also specific alleles that have been isolated and associated with genetic variations. For example, CYP2C9*2 is prevalent in 15 % of Caucasians, variably expressed in those of African descent, and not expressed in Asians. This suggests that individuals of Asian descent are much less likely to metabolize those medications metabolized by CYP2C9*2 effectively. Those of African descent are more heterogeneous in the activity of CYP2C9*2. The known variability in

Table 3.3 CYP450 metabolism activity on antidepressants and antipsychotics

CYP450		Mainly metabolized	Significantly metabolized	Partially metabolized
1A2	Antidepressants	Fluvoxamine	Clomipramine, duloxetine, imipramine	Amitriptyline, mirtazapine, trazodone
	Antipsychotics	Clozapine, olanzapine, thioridazine	Chlorpromazine	Haloperidol, thioridazine
2C9	Antidepressants	None	Amitriptyline, fluoxetine	Sertraline, venlafaxine
2C19	Antidepressants	Amitriptyline, citalopram, clomipramine, escitalopram	Doxepin, imipramine, nortriptyline, sertraline	Venlafaxine, trazodone
	Antipsychotics	None	Clozapine	Thioridazine
2D6	Antidepressants	Amitriptyline, desipramine, doxepin, fluoxetine, nortriptyline, paroxetine, venlafaxine	Bupropion, duloxetine, imipramine, trazodone	Citalopram, escitalopram, fluvoxamine
	Antipsychotics	Chlorpromazine, haloperidol, perphenazine, risperidone, thioridazine	Aripiprazole, olanzapine	Clozapine, quetiapine, ziprasidone
3A4	Antidepressants	Mirtazapine, trazodone, vilazodone	Citalopram	Sertraline, venlafaxine
	Antipsychotics	Haloperidol, quetiapine, ziprasidone	Olanzapine	Clozapine, risperidone

African descent is as follows: 1–3.6 % in African Americans, 4.3 % in Ethiopians, and 0 % in Beninese. On the other hand, CYP2C19 does not appear to be associated with racial or ethnic differences (Suarez-Kurtz et al., 2012).

CYP2D6 is responsible for the metabolism of over 100 medications including antipsychotics, selective serotonin reuptake inhibitors (SSRIs), and TCAs. CYP2D6 is highly polymorphic with greater than 70 variant alleles and more than 200-fold variability in metabolism. As noted by Xie, Kim, Wood, and Stein (2001), the poor metabolizer (PM) phenotype prevalence is as follows: 0.7–19 % in Africans, 5–10 % in Caucasians, and ~1 % in Asians. Additional studies have reported that the prevalence of PMs in African Americans ranges from 1.9 to 7.7 % (Marinac, Foxworth, & Willsie, 1995; Reling et al., 1991). Poor metabolizers are at risk of increased adverse effects with typically prescribed doses, while extensive metabolizers may require higher doses to achieve a therapeutic response. While most TCAs are substrates of CYP2D6, fluvoxamine, fluoxetine, and paroxetine are strong inhibitors of its activity. This is a concern when these TCA and SSRI medications are used in combination. The use of dose adjustments is relevant when a medication has a narrow therapeutic index, which is the range of serum level in which there are no effects versus therapeutic or toxic effects. A TCA is an example of such a medication (Horstmann & Binder, 2009).

As with antipsychotics, identification of PMs may prevent overdosing and increased risk of ADRs with TCAs and monoamine oxidase inhibitors (MAOIs) as well as potentially cardiotoxic effects of venlafaxine (Chen, Wang, Sun, & Young, 2003; Lessard et al., 1999). However, since SSRIs have a broad therapeutic window, there appears to be no clear dose-response relationship for depressive symptoms, toxic concentrations, or adverse effects (Horstmann & Binder, 2009). Therefore, identification of PMs is less relevant for other newer antidepressants such as the SSRIs. Understanding how an individual metabolizes a drug may also help determine the effect potential drug interactions could have on the individual.

According to Malik et al. (2010), those with certain CYP2D6 alleles are more likely to have

extrapyramidal side effects while on antipsychotics. This can lead to discontinuation of treatment. More than 70 % of whites, but only about 50 % of African Americans (as well as Asian or Sub-Saharan Africans) have functional CYP2D6 alleles that code for normal metabolic activity. This means that there is a high likelihood of decreased or non-functioning alleles in these populations. This will present as an increased risk of side effects "requiring lower doses for a therapeutic response to many medications when compared with European whites" (Malik et al., 2010, p. 796), including antipsychotics and antidepressants.

CYP3A4 is the most profuse P450 enzyme, representing greater than 50 % of liver metabolism, while CYP3A5 only represents 2 % of the total CYP3A grouping (Westlind-Johnson et al., 2006). The CYP3A family is highly variable across racial and ethnic groups, ranging from 40- to 50-fold (Ingelman-Sundberg, 2004). Many medications are metabolized by the CYP3A family as well as other CYP450 enzymes, which lead to difficulty attributing the variation to only the CYP3A family. In this family, the most common allele variant is CYP3A5*3. The prevalence in African Americans is 32 %, Caucasians is 90–93 %, East Asians is 73 %, Hispanics is 65 %, and South Asians is 60 % (Liu, Hao, Liu, Wang, & Xie, 2007; Xie, Wood, Kim, Stein, & Wilkinson, 2004). CYP3A4*1B may be a reason why the variability of CYP3A4 is very high between ethnic groups. The prevalence in Caucasians is 2–9 %, Hispanic Americans is 9–11 %, and African Americans is 35–67 %; however, the clinical impact of this variation has not been determined (Miura, Obua, Abbo, Kaneko, & Tateishi, 2009).

In a study by Bigos et al. (2011), the CYP3A4*3 genotypes were compared between Caucasians and African Americans. When comparing genotype carriers, Caucasians had the highest frequency of GG carriers (95 %), while African Americans were more commonly AA carriers (89%). AA carriers appear to have a 37 % higher clearance than GG carriers that correlates to a 48 % lower trough plasma concentration. These individuals were more likely to discontinue use of medication because of an inadequate response. CYP3A4*20 SNP is also highly variable among ethnic groups: 6 % in Caucasians, 26 % in African Americans, and 22 % in Asians. This variant appears to have no discernable activity (Wang, Guo, Wrighton, Cooke, & Sadee, 2011).

P-glycoprotein P-glycoprotein belongs to a highly conserved superfamily of ATP-binding cassette (ABC) transporter proteins. It plays a significant role in drug absorption and disposition. Genetic polymorphisms could affect p-glycoprotein's ability to influence intracerebral antidepressant substrate concentrations but not non-substrates.

A drug substrate is one that is metabolized by an enzyme system. For example, an inhibitor decreases the activity of the enzyme and possibly the metabolism of the substrate. In vitro experiments demonstrate that p-glycoprotein appears to regulate citalopram, sertraline, paroxetine, trimipramine, amitriptyline, nortriptyline, doxepin, and venlafaxine in the central nervous system (Horstmann & Binder, 2009). Two SNPs have been implicated in influencing the activity of P-glycoprotein resulting in differences in drug plasma concentrations of substrates (Hoffmeyer et al., 2000).

Genetic Associations

There is a large amount of evidence available for the dopamine receptor gene D2 (DRD2), dopamine receptor gene D3 (DRD3), and serotonin (5-HT)2A receptor and how their genetic polymorphisms relate to clinical response to treatment (Malhotra et al., 2004; Reynolds, Arranz, Templeman, Fertuzinhos, & San, 2006). D2 is the major site for antipsychotic action and 5-HT2A is the primary target suggested to differentiate second-generation antipsychotics (SGA) from FGA. Because these three genes explain only a small percentage of genetic variation, there are likely numerous other factors to consider when determining antipsychotic response.

In terms of clinical response, DRD2 and, to a lesser extent, DRD3 appear to influence positive symptoms, while the 5-HT2A receptor appears to

be more associated with negative symptoms. The val/met COMT polymorphism may be associated with effects on negative and cognitive symptoms by modulating frontal cortical dopamine activity and the glutamate metabotropic receptor-3 gene (Bishop, Ellingrod, Moline & Miller et al., 2005; Diaz-Asper, Weinberg, & Goldberg, 2006; Weickert et al., 2004). The promoter SNP, -1019C/G, on the 5-HT1A receptor gene appears to have a strong genetic association for negative and depressive symptoms and the response of risperidone and olanzapine; however, there was no association with positive symptoms of schizophrenia (Reynolds, Arranz et al., 2006; Reynolds, Templeman, & Godlewska, 2006).

The largest amount of data centers on the serotonin receptor SLC6A4, which is implicated in the effect of SSRIs, selective serotonin norepinephrine reuptake inhibitors (SNRIs), and TCAs. Although the clinical effects of SNRIs and TCAs may be associated with the SLC6A4 gene, SSRIs appear to be the group that experiences the highest rate of influence. The STAR*D study referenced earlier has provided the most abundant amount of data between the SLC6A4 association and SSRIs, specifically citalopram. The majority of this information focuses on the promoter region of SL6A4, also known as 5-HTTLPR. In the STAR*D sample, the response ranged from no effect on treatment remission in the homozygous sample to improved response in the white non-Hispanic group (Lesser et al., 2007; Mrazek et al., 2009). There may be an ethnic variability here as well, but the mechanism to explain these types of responses has yet to be determined.

Pharmacogenomic Basis for Adverse Effects

The effects of pharmacogenomics may be more significant for medication naïve patients compared to those on already established doses; therefore, limited evidence is available. The most noteworthy effects are for those individuals identified as poor metabolizers of a medication (Plesničar, Zalar, Breskvar, & Dolzzan, 2006). A link between the increased risk of TD and DRD3 and 5-HT2C receptor has been studied (Segman et al., 2000). The 5-HT2C receptor has the most well-established evidence to support the association with weight gain. The largest proportion of variation appears to be in medication naïve individuals (Templeman, Reynolds, Arranz, & San, 2005). One proposed mechanism for this effect is that antipsychotics interfere with the inhibitory effect of leptin, an anorexic hormone, on food intake. This could result from the antagonism of the 5-HT2C receptor in the hypothalamus (Templeman et al., 2005). Numerous studies have identified a genetic variation in human leukocyte antigens (HLAs) related to the increased risk of agranulocytosis with clozapine (Amar et al., 1998; Dettling, Cascorbi, Opgen-Rhein, & Schaub, 2007).

Pediatric Data

The pediatric data focus on stimulants, antipsychotics, and antidepressants because they are the most prescribed medications in child and adolescent psychiatry. As with adults, medications are chosen empirically based on the patient's symptom presentation, disease state process, potential adverse effects, cost, and patient and family experiences. As with any disease state, a portion of patients is treatment resistant. Although three-quarters of individuals respond to stimulant medication used in the treatment of ADHD, 25 % are considered treatment non-responders.

ADHD There is a large of amount of variability between treatment response, dosage, and tolerability in those children treated for ADHD. This variability appears to be related in the expression of the dopamine transporter gene (DAT1 or SLC6A3), the dopamine receptor genes (DRD2, DRD4), and to a lesser extent the alpha^2-adrenergic receptor (ADRA2A) and the norepinephrine transporter (SLC6A2). In ADHD, SLC6A3 is most often the target of pharmacogenomics studies focusing on ADHD and methylphenidate treatment.

Current research suggests the 10-repeat allele polymorphism at the DAT1 gene is associated with reduced methylphenidate efficacy (Froehlich

et al., 2011). In a study by Kirley et al. (2003) evaluating the effects of methylphenidate on neurocognitive function in stimulant-naïve subjects, the 10-repeat homozygous subjects exhibited better planning ability and better response inhibition compared to the 9-repeat carriers. Currently, there is no clear association of clinical response based on the dopamine transporter gene.

The next most commonly studied gene region is the DRD4. There are also inconclusive results regarding the effects of DRD4 on clinical response; however, the 7-repeat allele may be less responsive to dopamine than the 2-repeat and 4-repeat alleles (Asghari et al., 1995). Individuals without the 4-repeat allele and 4-repeat carriers appear to respond to methylphenidate better than those treated with placebo on hyperactive/impulsive scores (23 versus 40–49 %). The ADRA2A receptor, the main receptor in the noradrenergic system, appears to have a positive association with methylphenidate (MPH) and its clinical response, particularly the G allele. Over time, the G allele variant seems to be associated with a larger decrease of inattentive symptoms; however, in terms of MPH response, this variant was associated with higher levels of hyperactive/impulsive symptoms on placebo and as MPH doses increased (Froehlich et al., 2011). Yang, Wang, Li, and Faraone (2004) compared the G allele and T allele carriers. The results indicated the G allele induced a better MPH response, while the T allele carriers demonstrated improved impulsive behaviors. It has been suggested that T allele carriers may have lower norepinephrine transporter (NET) levels in the brain. These lower levels may explain the better MPH response because of having to block fewer NET to achieve response. While the literature for ADHD pharmacogenomics continues to grow, difficulty remains with extrapolating the effects of each gene on clinical response.

Autism Spectrum Disorders Most pharmacogenomic pediatric data associated with antipsychotics has been researched in the context of autism spectrum disorders. Correia et al. (2010) studied associations between the 5-HT2A, DRD3, 5HT2C, and the ATP-binding cassette, subfamily B (ABCB1) polymorphisms and risperidone used in the treatment of autism. The results indicated that these polymorphisms were predictors of improved clinical response with risperidone. In addition, the study determined that the 5HT2C and 2D6 polymorphisms may be associated with increased BMI and waist circumference, while 5HT2A, 5HT2C, HTR and brain derived neurotrophic factor (BDNF) may influence prolactin elevations. Decreased BMI and waist circumference were observed in the CYP2D6 ultrarapid metabolizer phenotype compared to the extensive metabolizer phenotype. The sample studied was 97.8 % ($n=44$) Caucasian and 2.2 % ($n=1$) African American. Evidence is still evolving as to the implications of pharmacogenomics and the effects on the pediatric population of antipsychotics.

To date, there have been limited pharmacogenomic studies in children and adolescents on antidepressants. In the pediatric population, the data are so negligible that a clear correlation between clinical response and the SLC6A4 or 5-HTTLPR cannot be identified.

Overall, several conclusions can be drawn about polymorphisms. First, polymorphisms are only relevant when the result is large differences between poor and extensive metabolizer phenotypes. Second, pharmacokinetic differences are important when medications have a narrow therapeutic index. Third, if medications are adjusted based on clinical response, phenotypic differences will be corrected automatically. Finally, medications that are prescribed to a larger portion of the population are at risk for greater implications (Burroughs, Maxey, & Levy, 2002).

Pharmacogenomic Testing

Pharmacogenomic testing is a new endeavor that is being explored. The goal of commercial testing is to help provide an understanding of the relationship between drug plasma concentration and efficacy. However, it is difficult to routinely recommend pharmacogenomic testing as the evidence for its use is still evolving. The role of pharmacogenomics in helping to determine treatment planning appears to emerge after the failure of, at

minimum, two medication trials or if clear evidence of an unusually higher rate of adverse effects occurs at recommended doses.

Adherence

The pharmacogenomic correlation between ethnicity, race, and pharmacodynamic response to psychotropic drugs remains elusive. Currently, the potential clinical application of genetic research to psychiatric diagnoses is difficult even if applied to a theoretical homogenous reference population. Inherent cultural biases in the mental health system can interfere with the evaluation and management of patients (Chap. 7). This may impact the accuracy of diagnoses, appropriateness of treatment, adherence to the agreed upon treatment plan and reinforce apparent ethnic or racial differences in response to care.

The decision to take prescribed medication is multifactorial. The practice of pharmacotherapy includes the therapeutic relationship, which is fundamental for its efficacy. This relationship is inherently more complex in work with youth because of the presence of the parent/guardian, an additional, but necessary factor (Pruett & Martin, 2003). An understanding of therapeutic adherence literature is helpful in this process. We will review the major psychosocial factors that contribute to medication adherence. As in the rest of this chapter, we continue to extrapolate from the general literature as well as the African American and pediatrics literature on chronic illness. In addition we will draw from the literature on adherence in general/adult psychiatry.

Mental Health Literacy

Mental health literacy, which contributes to adherence, is the "knowledge and beliefs about mental disorders which aid their recognition, management or prevention" (Jorm, 2000, p. 396). This includes the ability to recognize psychological distress or disorders, understand risk factors, causes and available treatments, having attitudes that foster help seeking and knowing how to obtain information about mental health. In their review, Stewart et al. (2012) noted that health literacy might be lower in children and adolescents from diverse groups (Chandra et al., 2009). As such, they concluded that if the practitioner does not educate or ask about side effects, the risk of non-adherence might increase.

General Adherence

Adherence is a vital factor to consider in the use of medications. From one-third to 69 % of all medication related hospital admissions per year are due to poor adherence (Osterberg & Blaschke, 2005). Adherence to treatment for chronic disease is about 50 % in developed countries and is lower in developing areas (Sabaté, 2003). The World Health Organization (WHO) defined adherence as "the extent to which a person's behaviour – taking medication, following a diet, and/or executing lifestyle changes, corresponds with agreed recommendations from a health care provider" (Sabaté, 2003, p. 3). This is in contrast to compliance, which does not require a patient's agreement with the recommendations and minimizes autonomy.

The WHO conducted an adherence project, assessing the worldwide problem of adherence with treatments for diseases such as asthma, depression, diabetes, HIV/AIDS, hypertension, and cancer (palliative care). They found that patients require support in taking medication, instead of blame for not doing so. They also identified social, economic, and patient related factors, as well as characteristics of the health care team and health care system itself, that impact adherence. The patient's readiness for medication is a significant factor, and health care providers must be able to assess, guide, and follow this level of readiness. Peer support by other patients impacts adherence as well.

A multidisciplinary approach to adherence is recommended and members of the team (including psychiatry, pharmacy, nursing, psychology, social work, and others) should be trained about how to enhance adherence. Education about the medication, using the lowest possible frequency

of dosing, and tailoring prescriptions to the patient's needs are helpful to increase adherence. Managing comorbidities and personality traits with counseling and psychotherapy are also key to adherence. Furthermore, unless adherence is specifically discussed, 30–40 % of patients will stop their medications after about 12 weeks, regardless of whether they perceive benefits from the medication (Sabaté, 2003).

In order to manage poor adherence, it must first be clearly assessed by simply asking the patient and caregiver about any problems with taking the medication, or anticipating any such problems. This should occur even if the patient appears to be adherent. Counting pills, using pharmacy records, smart pill containers, and medication levels are recommended to help increase adherence (Velligan et al., 2010a).

Adherence in Children

Smith and Schuchman (2006) noted that managing non-adherence is as important as any other aspect of treatment of chronic illness, adding the developmental aspect that adherent children are at risk for non-adherence as adolescents. The term adherence encompasses "medication taking, complying with dietary rules or other lifestyle modifications, blood work, and clinic appointments" (p. 614). When adolescents are asymptomatic for long periods, they are less likely to remain adherent. Routine assessment of adherence and specifically targeting non-adherence when it is present is recommended (Smith & Schuchman, 2006). Children benefit from oral dosage forms of medications that are easier to swallow, better tasting, or smaller pills (Zajicek et al., 2013).

The Health Belief Model

The Health Belief Model (HBM) requires an understanding of the patient's assessment of the seriousness of his disorder. We know that parental beliefs/knowledge about ADHD impact their decision to seek treatment for their children (Bussing, Schoenberg, & Perwien, 1998). For example, the perception of ADHD in Caucasian parents is more likely to be "this requires professional assistance," but in African American families it is more likely to be "I don't want my child labeled –I don't want him to stand out" (Charach, Volpe, Boydell, & Gearing, 2008).

An accurate understanding of a disorder may contribute to one's appreciation of the benefits of intervention, decisions to seek treatment, and adherence to agreed upon plans of care. This is noted in the HBM (Jones, Smith, & Llewellyn, 2014). The Beliefs about Medicine questionnaire (Horne, Weinman, & Hankins, 1999) assesses a patient's beliefs about medications that may contribute to non-adherence, citing social cognition models including HBM and others (Horne et al., 1999). This may be a helpful addition to the clinician's toolkit in managing adherence.

Chronic Medical Conditions in Children

There is a robust literature on the management of chronic illnesses such as asthma, diabetes, and HIV in adolescents (Bean et al., 2014; Belzer et al., 2014; Bruzzese, Idalski Carcone, Lam, Ellis, & Naar-King, 2014; Mosnaim et al., 2014; Ogedegbe et al., 2008; Saberi, Yuan, John, Sheon, & Johnson, 2013). As many psychiatric disorders, such as ADHD, depression, and bipolar disorder may require chronic use of medication as well as psychotherapy, this literature may be useful to consider in improving adherence with youth and their families in managing mental illness.

In a meta-analysis of adherence in medications prescribed by nonpsychiatric physicians, DiMatteo (2004) found that adolescents were less adherent than children, girls were more adherent than boys and that adherence is positively correlated with education and income. Overall, they found that non-adherence occurs in 24.8 % of patients. Of note, there was no gender difference observed in adults on adherence.

In adolescents, chronic illnesses such as asthma, epilepsy, and diabetes have poor medication adherence as clearly illustrated in a study of

adherence to Continuous Positive Airway Pressure (CPAP) treatment for obstructive sleep apnea (Prashad et al., 2013). Adolescent rebellion against authority may factor into non-adherence with medication use. Factors that had a significant role in increasing adherence were consistent levels of structure in the home, recognition of the benefits of using CPAP (and the risks of not using it), as well as the mode of communication in the family. Adolescents with high adherence had more authoritative parents and accepted their explanatory and helpful reminders to use their CPAP. Those with low/no adherence had more authoritarian parents and felt that their parents yelling about CPAP indicated they did not understand how difficult it was to use (Prashad et al., 2013).

Bruzzese et al. (2014) studied African–American adolescents with asthma in relation to adherence in relation to the usefulness of the self-determination theory. This theory postulates that an individual is most likely to adhere when needs for autonomy, competence, and relatedness are met. Incorporating asthma medication administration into the family routine resulted in improved adherence to the agreed-upon treatment. Education regarding inhaled corticosteroids was helpful in increasing adherence in both African American and Latino adolescents with asthma. Increased patient age was not associated with adherence improvement (Mosnaim et al., 2014).

Simply forgetting was a major reason for non-adherence with antiretroviral treatment in a study of HIV positive adolescents and young adults described as very stressed and marginalized. Cell phone social support and telehealth interventions have been effective in increasing adherence in this population (Belzer et al., 2014; Saberi et al., 2013).

Adult Adherence in Psychiatric Illness

General risk factors for non-adherence in mental illness include co-morbid substance dependence, poor insight, denial of the illness, and a poor attitude toward the medication, including feeling that the medication cannot help (Julius, Novitsky, & Dubin, 2009). Experiencing side effects and a lack of family support to take the medication are also contributing factors to non-adherence (Julius et al., 2009). When there is a racial difference between the therapist and patient, Larrison, Schoppelrey, Hack-Ritzo, and Korr (2011) found that the only factor that made a difference in adherence was the amount of positive experiences the clinician had previously with individuals racially/ethnically different from themselves. This should be generalizable to medication management situations as well.

A consensus survey of experts working with patients with schizophrenia and bipolar disorder listed numerous strategies to enhance adherence in the severely persistent mentally ill population (SPMI) (Velligan et al., 2010b). They noted that cognitive behavioral therapy (CBT) techniques are useful to help the patient's understanding of the treatment. Compliance therapy (CT) is a CBT technique that melds psychoeducation and motivational interviewing (MI) techniques. CT focuses on the relationship between non-adherence and relapse. However, the results are mixed. Family-Focused Therapy has also been found to increase adherence (Picardi & Gaetano, 2014).

Interpersonal and social rhythm therapy (IPSRT; Frank, Swartz, & Boland, 2007; Velligan et al., 2010b) improves adherence and prevents relapse. It has also been adapted for use with adolescents with bipolar disorder (Frank et al., 2007; Hlastala, Kotler, McClellan, & McCauley, 2010). This therapy focuses on stabilizing daily routines and resolving interpersonal problems incorporating MI and CBT skills. The increased frequency of visits including psychoeducation for the patient and family in this therapeutic approach are additional strategies to improve adherence (Velligan et al., 2010b). Managing side effects, addressing specific reasons for non-adherence, and ensuring the use of appropriate psychopharmacology are key to improved adherence in IPSRT. Family-Focused Therapy involves 21 sessions over a 9-month period and includes psychoeducation, including discerning the difference between development and the mental illness, assessment of health beliefs, communication skills, and problem solving (Miklowitz, 2006; Picardi & Gaetano, 2014).

Involuntary outpatient commitment and environmental monitoring of medication use with tools such as checklists, signs, electronic reminder devices, and other forms of information technology are helpful. Additional strategies such as psychoeducation, Assertive Community Treatment (ACT) teams, and case managers are additional strategies useful in improving adherence. In psychoeducation, the family and patient are taught more about the illness as well as the medication. ACT teams involve the use of clinical support teams that come to the patient to improve compliance.

Adherence in African Americans

Stigma It has been noted that African Americans and Latinos are less likely than White Americans to utilize mental health care (Cook, McGuire, & Miranda, 2007). This is true even when the care is covered by insurance (Thomas & Snowden, 2001). Carpenter-Song et al. (2010) interviewed 25 adult inner-city residents with severe mental illness about their attitudes regarding their illness and treatment. The African American patients were found to have stigma as a prominent theme, and considered severe mental illness to be "private family business." Perceptions of their illness were not as "biomedical" as those of the White American participants. African Americans did not have the same level of wariness of the diagnostic label as the Latino participants in the study. African American families are more likely to seek assistance from spiritual leaders rather than health care specialists for psychiatric issues. This number may be even higher in rural communities with limited access to mental health providers. There is a significant amount of poverty in this population contributing to concerns about cost. One-third of rural African Americans felt that white professionals could not understand the problems of African American families. The recommendation was made to educate clergy about mental health needs and help clergy and mental health professionals work together.

Stigma surrounding the diagnosis and treatment of mental illness may delay the treatment of first-episode psychosis (Franz et al., 2010). Schizophrenia is very highly stigmatized (Anglin, Link, & Phelan, 2006) and this causes delays in seeking help, poor engagement in treatment, and under-treatment of affected individuals (Broussard, Radkins, & Compton, 2014).

Factors Decreasing Adherence

Adherence in a community mental health setting has been found to be lower in African American patients compared to Whites (Diaz, Woods, & Rosenheck, 2005). Over 50 % of minority patients terminate counseling after their first contact with a therapist, but only 30 % for whites (Sue & Sue, 1999). African American patients begin an assessment of the therapist with the first session. They judge whether there is a client–therapist match, assessing the degree of safety with the therapist, and the effectiveness of the encounter. If this assessment is negative, it was likely that future interactions would be more superficial, or the client would terminate the relationship (Ward, 2005).

African Americans are most likely to express concern about fear of racial discrimination, stigma/labels, impact on employment, and privacy when considering participation in psychiatric genetic studies (Nwulia et al., 2011). In the infamous Tuskegee Study, the progression of untreated syphilis in African American men over decades, despite the existence of treatment and patients enrolled absent informed consent, is often cited as a major source of distrust of African Americans in medical research. Other potential reasons why African Americans may refuse study participation include a general distrust of government, fear of mistreatment, and exploitation (Yancey, Ortega, & Kumanyika, 2006).

Ayalon, Areán, and Alvidrez (2005) studied elderly Black and Latino patients taking antidepressants prescribed by their primary care provider. This study revealed that intentional non-adherence was related to concerns about side effects, stigma associated with the medication, and the perception that the antidepressants were less important than their other medications.

Unintentional non-adherence was associated with cognitive impairment. In a homeless adult population, African American patients were less likely to adhere to behavioral therapy or psychiatric appointments (Moczygemba, Osborn, & Lapane, 2014). In working with African American adults with anxiety disorders, it has been noted that African Americans have less favorable attitudes towards both psychotherapy and pharmacotherapy—assessing patient attitudes and beliefs is important to maximize the benefit of recommended treatment (Wagner et al., 2005).

Factors Improving Adherence

Motivational interviewing (MI) has been found to be useful in increasing adherence in managing hypertension and obesity (Bean et al., 2014; Ogedegbe et al., 2008) in African American adults. MI is a patient-centered means of enhancing motivation for change through identifying and resolving ambivalence towards treatment with the patient. An individual may progress from an early stage of indicating a lack of readiness for change to one of joyous excitement that the change is proceeding well.

The pros and cons of making a change are reviewed with the patient at the initiation of the process. The clinician moves along at the patient's pace. If the clinician begins to recognize resistance by the patient, this may indicate that the process is moving too fast. The patient's level of motivation must be reassessed and the pace adjusted accordingly. In MI, adherence is conceptualized as a coping behavior—the patient understands the illness and beliefs regarding the medication. There is an inherent connection between adherence and a decrease in symptoms and improvement in personal health. The clinician asks open-ended questions, engages in active listening, and reflects on the patient's thoughts and summarizes to help the process and progress to continued change (Julius, 2009).

Cruz et al. (2013) found that for outpatient medication check appointments psychiatrists whose voices conveyed friendliness, warmth and empathy had better adherence with appointments for both African American and White patients with depression. In a review of the literature on adherence for African American and Latino populations, no one intervention was found to be universally successful. However, MI was particularly useful for some African American patients in studies of interventions with HIV infection, hypertension, and asthma.

Attention Deficit Hyperactivity Disorder

ADHD is a chronic illness; as such, adherence is not uncommon. African American adolescents and their families are more likely than Whites to have misperceptions regarding etiology and medication overuse in regards to ADHD. Such misperceptions could impact beliefs about the disorder and adherence with recommended treatment. Culturally appropriate psychoeducation strategies for this population are recommended (Bussing et al., 2012).

In their review of studies of adherence among patients with ADHD, Gajria et al. (2014) found that the continuous use of prescribed stimulants was poor, and averaged 136 days for children or adolescents, and 230 days for adults. They identified side effects, poor symptom control, inconvenient dosing, and the social stigma of taking medication as the primary reasons for discontinuation. Patient attitude and patient physician-communication were also significant factors that decreased adherence. They also noted that half of all patients were non-adherent within 2–3 years of starting medication. Physician assessment of African American youth had lower rates of adherence compared to Western European youth. Children and adolescents were more likely to adhere to non-stimulant than to stimulant medications. Specific factors contributing to non-adherence with non-stimulants were not discussed.

Gajria et al. (2014) found that in North America, the most common reasons for stopping medications were untoward effects, poor symptom control, inconvenient dosing, stigma related to taking medication, and the patient's attitude

about the medication. They recommended psychoeducation for caregivers and parents use of longer-acting preparations and specifically checking with patients to ensure that the medication is still effective. This review did not provide more specific information about African American youth, however. They noted a need for further research on adherence with the use of non-stimulant medications.

Hervey-Jumper, Douyon, and Franco (2006) noted that ADHD is often undiagnosed and therefore untreated in African Americans. This results in "higher rates of delinquency, incarceration, teen pregnancy and sexually transmitted diseases associated with inadequate or delayed treatment of ADHD" (p. 233). There is a higher risk of learning difficulties and earlier onset of substance use disorders. While teachers may identify symptoms consistent with ADHD, parents may have difficulty accepting this as a possible diagnosis with the accompanying recommendations for pharmacological intervention. If a parent believes that diet is the etiology, this is the path the parent will take instead. Many African American parents tend to have less knowledge about ADHD than Caucasian parents (Bussing et al., 1998, 2012). Parents may worry about stigma and the "label" of ADHD, telling children "we don't air our dirty laundry," or "we don't put our business in the street" (Murry, Heflinger, Suiter, & Brody, 2011). Taking medications may be seen as a sign of weakness, or the first step in becoming addicted to pills. There is also a concern that the child will have to take medication for the rest of his or her life.

Conclusions

Research on efficacy and side effects with sizable numbers of ethnic minority participants is still quite limited. There is as much heterogeneity within an ethnic or racial group as there is between groups. This makes research in the minority populations difficult. The lack of consistent findings emphasizes the importance of including both adult and pediatric racial and ethnic minorities in clinical trials in sufficient numbers to draw inferences regarding race and ethnicity. Failing to do so leaves minorities at potentially increased risk for idiosyncratic side effects as well as ineffective or toxic dosing. Until this is done, evidence-based treatment guidelines will not be able to be developed to enhance the psychopharmacologic treatment of African American youth. This, coupled with genetic variability in psychopharmacologic response to psychotropic drugs may play a role in adherence to treatment decisions made by patients, parents, and clinicians.

In terms of the pediatric African American population, extrapolation of the available information may lead to variable conclusions on pharmacokinetic and pharmacodynamics processes. Although the pharmacodynamics data are the most robust for ADHD and ASDs, there is no information on the effect of different ethnicities in pediatrics on these processes. This lack of data makes it difficult to fully understand the impact of pharmacogenomics on the pediatric African American population. As pharmacogenomics is a continually developing science, the ability to extrapolate information between ethnicities and age-specific populations will continue to evolve. Future research will need to focus on the evolution of pharmacogenomics in the child and adolescent mental health population. For now the role of ethnicity will continue to be extrapolated from adult data.

The overall recommendations for adherence are not culture specific. Stigma must be recognized and addressed, the therapeutic relationship must be fostered, and medication adherence must be specifically mentioned and reviewed with the patient in every session. Stigma and poor mental health literacy are correlated and must be explored to decrease disparities in the use of mental health services.

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