Pharmacogenomics and Psychiatric Clinical Care

ABSTRACT

Approximately one in five individuals in the United States experiences mental health issues in any given year, and these disorders are consistently among the leading causes of years lived with disability. Unfortunately, many mental illnesses are lifelong conditions that require medication and therapy to improve quality of life, yet clinical trial data show that many patients fail to achieve remission or require several pharmacological interventions prior to remission. These results indicate a need to address the variability among patients in their response to medication, in addition to developing treatment plans tailored to the individual. One approach that may help explain patient variability in response to medication is pharmacogenetic testing. The current review shows the clinical use of pharmacogenetic testing in a small subset of gene variants and how they pertain to psychiatric illness and treatment. Recent evidence suggests that genetic testing for psychiatric illness can improve patient outcomes in addition to decreasing health care costs. [*Journal of Psychosocial Nursing and Mental Health Services, 56*(1), 22-31.]

A 2014 survey conducted by the Substance Abuse and Mental Health Services Administration (SAMHSA; 2015) estimated that 18.1% of adults in the United States experience some form of mental illness, defined as any mental, behavioral, or emotional disorder in the past year that met criteria in the fourth edition (text revision) of the *Diagnostic and Statistical Manual of Mental Disorders* (American Psychiatric Association, 2000). Furthermore, 4.1% of these individuals (or 9.8 million people) were estimated to have a serious mental illness (i.e., substantially interfered with or limited one or more major life activities) (SAMHSA, 2015). Unfortunately, many mental illnesses are lifelong conditions that require proper medication and therapy to improve quality of life (Connell, Brazier, O'Cathain, Lloyd-Jones, & Paisley, 2012). The Global Burden of Disease Study 2010, a collab-

Russell J. Amato, PhD; Joseph Boland, MS; Nicole Myer, PhD; Lauren Few, PhD; and Daniel Dowd, PharmD

orative project led by the Institute for Health Metrics and Evaluation at the University of Washington, observed that mental and substance use disorders are consistently among the leading causes of years lived with disability (YLD; i.e., years of productive life lost due to disability) (GBD 2015 Disease and Injury Incidence and Prevalence Collaborators, 2016; Murray et al., 2013; Vos et al., 2012). In addition to YLD, there is a large economic burden associated with mental illness. A recent study (Roehrig, 2016) noted that the cost associated with treating mental illness was approximately $201 billion in the United States alone, and that these costs exceeded those for cardiovascular disease, trauma, and cancer (Insel, 2008). Taken together, these data suggest a growing need to improve mental health treatment due to losses in quality of life for patients, as well as the large economic impact on patients and the health care system as a whole.

Despite the development of new and promising pharmacotherapies for mental health disorders, large-scale clinical studies have shown disappointing results in disease remission. Some seminal studies include the Sequenced Treatment Alternatives to Relieve Depression (STAR*D) trial, the Clinical Antipsychotic Trials of Intervention Effectiveness (CATIE) study for schizophrenia, and the Systematic Treatment Enhancement Program for Bipolar Disorder (STEP-BD) (Lieberman et al., 2005; Rush et al., 2006; Thase, 2007). One example highlighting this issue can be seen in initial remission rates in the STAR*D trial for depression. Only 37% of patients using first-line treatment (i.e., treatment as usual) achieved full remission, and remission rates decreased with each subsequent medication trial. These results indicate a need to address the variability among patients in their response to medication, in addition to developing treatment plans tailored to the individual. A relatively new approach for explaining patient variability in response to medication is *pharmacogenetic testing*—genetic testing for variant alleles associated with disease or medication response. Genetic testing has been used and shown to be effective in cost savings and treatment responses in nonpsychiatric disorders (e.g., metabolic, hematologic, cardiovascular), with the prototypical example being genetic testing for breast cancer susceptibility gene variants (e.g., BRCA) seen in patients with a hereditary predisposition for breast cancer (Hamilton, 2009; Manchanda et al., 2014). Recent evidence suggests that genetic testing for psychiatric illness can also be effective for improving patient outcomes in addition to decreasing health care costs (Brennan et al., 2015; Fagerness et al., 2014; Gardner, Brennan, Scott, & Lombard, 2014; Winner, Carhart, Altar, Allen, & Dechairo, 2013).

The current review illustrates the clinical use of pharmacogenetic testing in psychiatry using a small subset of gene variants and examines their relationship to symptomatology, pharmacokinetics, and response to treatment.

GENES ASSOCIATED WITH SYMPTOMATOLOGY

Catechol-O-Methyltransferase (COMT)

COMT is one enzyme responsible for the breakdown of dopamine and is critical in the frontal lobes of the brain, where dopamine transporter activity is low (Apud & Weinberger, 2007). Dopamine levels in this area of the brain are essential for memory, attention, judgement, and other executive functions (Cools, 2008). A single nucleotide polymorphism (SNP) at position rs4680 of this gene can change the function of the encoded enzyme by affecting its protein structure, which in turn affects its capacity to metabolize dopamine (Lotta et al., 1995). An adenine nucleotide at this position codes for a methionine amino acid (Met) at positions 108 in the soluble form of COMT and 158 in the membrane bound form of COMT, whereas a guanine at this position codes for the amino acid valine (Val) at these same positions (Lachman et al., 1996). Individuals homozygous for the Met allele have reduced enzymatic activity and higher dopamine levels, whereas individuals homozygous for the Val allele have increased enzyme activity and lower dopamine levels (Apud & Weinberger, 2007). Clinical studies have shown that humans with the Val/Val genotype may have deficits regarding cognitive function, memory, attention, motivation, and judgement (Barnett, Jones, Robbins, & Müller, 2007; Cools & D'Esposito, 2011; Frank & Fossella, 2011; Sheldrick et al., 2008), whereas the Met/Met genotype may be associated with superior executive functioning. In Val/Val carriers, dopaminergic agents, including the COMT inhibitor tolcapone, have been shown to improve executive function and working memory in animals and humans (Apud et al., 2007; Apud & Weinberger, 2007; Hamidovic, Dlugos, Palmer, & de Wit, 2010; Lindenmayer et al., 2015). However, COMT inhibitors and dopaminergic stimulants may produce a deleterious effect on cognition in Met/Met patients (Apud et al., 2007; Mattay et al., 2003). More specifically, Mattay et al. (2003) found that amphetamine enhanced prefrontal cortical efficiency as assayed by functional magnetic resonance imaging in Val/Val individuals, and produced deficits in working memory in Met/Met carriers. A study by Parasuraman et al. (2014) investigating more complex behavior with real-world applicability found that Met/Met carriers piloting unmanned vehicles had an increase in the number of enemy targets destroyed and a greater reduction in enemy red zone incursions in a supervisory control task, which could have implications for personalized military training.

There is recent evidence that the COMT Met/Met genotype is associated with anxiety-related disorders, with posttraumatic stress disorder being the most extensively studied (Boscarino, Erlich, Hoffman, & Zhang, 2012; Nor-

rholm et al., 2013). A meta-analysis by Pooley, Fineberg, and Harrison (2007) found an association between COMT Met allele carriers and obsessive-compulsive disorder (OCD), but this association was only found in males. These data indicate that COMT may play a role in the sexual dimorphism associated with OCD. In addition to being associated with anxiety disorders, a study in healthy participants by Baumann et al. (2013) found a correlation between the COMT Met/Met genotype, aversive life experiences, and general anxiety sensitivity, indicating this genotype may play a role in the development of these disorders. Taken together, these data indicate COMT genotype may play a role in executive function and susceptibility to anxiety disorders.

Calcium Channel, L-type Voltage-gated, Alpha-1C Subunit (CACNA1C)

CACNA1C is important in the regulation of calcium signaling (Harrison, 2016; Yoshimizu et al., 2015). Several genome wide association studies (GWAS) have identified a variant in this gene, the "A" allele, which is associated with conditions including schizophrenia, bipolar disorder, and major depressive disorder (Bhat et al., 2012; Erk et al., 2014; Ferreira et al., 2008; Gonzalez et al., 2013; Green et al., 2010; Ivorra et al., 2014; Nie et al., 2015; Psychiatric GWAS Consortium Bipolar Disorder Working Group, 2011; Rao et al., 2016; Szczepankiewicz, 2013). Variations in this gene may lead to ion channel dysfunction, resulting in a prolongation of the period during which the calcium channel pore remains open and leads to increased excitatory signaling (Bhat et al., 2012; Yoshimizu et al., 2015). It has also been reported that this variant is associated with changes in amygdala volume (Lancaster, Foley, Tansey, Linden, & Caseras, 2016), frontal-hippocampal function (Erk et al., 2014; Paulus et al., 2014), disruptions in cognition in patients with schizophrenia (Hori et al., 2012) and bipolar disorder (Soeiro-de-Souza et al., 2013), and abnormal glutamatergic signaling (Brewer et al., 2007). Although the association with this variant and treatment response has not been fully elucidated, several drug classes, including calcium channel blockers, mood stabilizers, atypical antipsychotics, and omega-3 fatty acids, can reduce calcium channel signaling and excitatory neurotransmission (Casamassima et al., 2010; Chertkow, Weinreb, Youdim, & Silver, 2007; de Bartolomeis, Avvisati, Iasevoli, & Tomasetti, 2013; Hallaq, Smith, & Leaf, 1992; Mizoguchi, Kato, Horikawa, & Monji, 2014; Ortner & Striessnig, 2016; Rapoport, Basselin, Kim, & Rao, 2009). Calcium channel blockers, such as verapamil, isradipine, and nimodipine, have been shown to attenuate psychiatric symptoms in several clinical studies (Hollister & Trevino, 1999; Krupitsky et al., 2001; Ostacher et al., 2014; Taragano, Bagnatti, & Allegri, 2005). However, most research investigating these drugs and how they interact with calcium channel variants has focused on treatment response in cardiovascular disease (Beitelshees et al., 2009). Mechanistically, mood stabilizer drugs, atypical antipsychotic agents, and omega-3 fatty acids have been shown to modulate calcium signaling and neuronal excitability. Drugs such as pregabalin and gabapentin have also been shown to reduce symptoms of anxiety, likely due to a calcium-related mechanism (Stahl, 2004).

...Catechol-O-methyltransferase genotype may play a role in executive function and susceptibility to anxiety disorders.

Dopamine Receptor D2 (DRD2)

DRD2 is a G protein-coupled receptor (G_i) that inhibits adenylyl cyclase activity (Usiello et al., 2000) and is involved in movement, perception, and drug abuse. Most neuroleptic agents act through blockade of D2 receptors to inhibit dopamine signaling, and affinity for this receptor has been shown to correspond to risk for, and degree of, side effects with these medications (Naumovska et al., 2015). Deletion (Del) of a cytosine in the promoter region at position –141 reduces gene expression and binding affinity in vitro, resulting in reduced D2 receptor density (Arinami, Gao, Hamaguchi, & Toru, 1997; Lencer et al., 2014; Naumovska et al., 2015). This mutation has been associated with an increased risk for poor response and adverse events with antipsychotic medications (Lencz et al., 2010; Zhang, Lencz, & Malhotra, 2010), in addition to increased risk for opioid dependence (Chen et al., 2011). A study by Li et al. (2002) found a positive association between nasal-inhaled heroin use and the –141C Insertion (Ins)/Del DRD2 polymorphism in Chinese patients. In addition to opioid dependence, there is some, albeit conflicting, evidence that the –141C Del variant is associated with ethanol dependence (Gelernter & Kranzler, 1999; Prasad, Ambekar, & Vaswani, 2010). Concerning treatment response, a study by Lerman et al. (2006) suggested that the –141C Ins/Del polymorphism may influence whether bupropion or nicotine

replacement therapy (NRT) would be more effective for tobacco dependence. The investigators found that bupropion was more effective for patients who were homozygous for the Ins allele, whereas NRT seemed to be more helpful for patients who were Del allele carriers. Taken together, these data suggest a role for DRD2 –141C Del variant in not only the response to antipsychotic medication, but substance use disorders and treatment selection.

GENES ASSOCIATED WITH PHARMACOKINETICS

P-Glycoprotein (ABCB1)

P-glycoprotein (P-gp), encoded by the ABCB1 gene, is an efflux pump responsible for energy-dependent transport of a number of drugs and endogenous compounds out of the cell. Depending on the tissue, these pumps can affect drug absorption (e.g., intestinal lining), distribution (e.g., blood–brain barrier), and excretion (e.g., proximal tubules of the kidney) (Hodges et al., 2011). This gene has >120 polymorphisms, but only a handful have shown any predictive validity for response to antidepressant agents (Brückl & Uhr, 2016). A recent review by Brückl and Uhr (2016) identified two candidate SNPs in particular (rs2032583 and rs1045642) that were more consistently associated with either clinical efficacy or risk for side effects to antidepressant substrates of P-gp. For example, carriers of the intronic SNP rs2032583 (T→C) were approximately five times as likely to remit after 4 weeks of treatment with antidepressant agents and this effect was specific for the P-gp substrates citalopram, venlafaxine, and d-venlafaxine (Uhr et al., 2008). Homozygotes of the SNP rs1045642 C→T (i.e., C3435T) needed only half the dose of escitalopram (11 mg) when compared to C/C homozygotes and C/T heterozygotes (19 mg and 24 mg, respectively) to achieve remission. In addition, the same study found that 73% of T/T carriers remitted on venlafaxine, whereas only 12% of the C/C genotype remitted. There is also evidence that this same mutation (rs1045642 C→T) in ABCB1 is a risk factor for opioid dependence, which may be due to increased permeability of opioid agents to the blood–brain barrier (Beer et al., 2013). These data suggest that genetic variants of ABCB1, which impact drug absorption and brain penetration, may play a role in patient response to medications that are P-gp substrates.

Cytochrome P450s (CYP450): 1A2, 2C19, 2D6

CYP450s are a family of hepatic enzymes that are responsible for the metabolism of a large number of psychotropic (and non-psychotropic) medications, and variations in the genes encoding these enzymes can result in increased exposure (poor or intermediate metabolizers) or decreased exposure (fast and ultra-rapid metabolizers) of pharmacological substrates (Ingelman-Sundberg, Oscarson, & McLellan, 1999). Unfortunately, for patients with these variants, the resultant variation in exposure may be accompanied by alterations in medication efficacy and adverse effects. To add another layer of complexity to drug metabolism, many CYP450 enzymes can be induced (i.e., increased expression of the enzyme) or inhibited by other pharmacological agents, which can also alter drug serum levels (Pelkonen, Maenpaa, Taavitsainen, Rautio, & Raunio, 1998). CYP1A2 is unusual in that it is also highly inducible by environmental factors such as smoking (nicotine and marijuana) and the consumption of cruciferous vegetables/chargrilled meat (Murray et al., 2001; Nebert, Dalton, Okey, & Gonzalez, 2004). The *1F variant of the enzyme can exacerbate this risk of induction (Sachse et al., 2003). Smoking as few as seven tobacco cigarettes per day or two marijuana cigarettes per week can dramatically induce expression of this gene, resulting in increased clearance rates (2- to 3-fold) and reduced exposure of drugs that are metabolized by this enzyme (e.g., theophylline, duloxetine, fluvoxamine, clozapine) (Haslemo, Eikeseth, Tanum, Molden, & Refsum, 2006; Jusko et al., 1979; Plowchalk & Rowland Yeo, 2012).

Pharmacogenetic testing of CYP450s can offer clinical use in regard to dosing, in addition to also reducing the number of emergency department visits for patients taking CYP450 substrates (Kitzmiller, Groen, Phelps, & Sadee, 2011). As a result, regulatory agencies (e.g., U.S. Food and Drug Administration [FDA]) include warnings in the prescribing information of many pharmaceuticals to alert prescribers about the potential for variable exposure in individuals with certain genotypes. More than 120 drugs, including many commonly used psychotropic agents, include such warnings. For example, the citalopram package insert states that the dose should not exceed 20 mg per day for poor metabolizers of CYP2C19, as increased serum level can cause QTc prolongation (Sheeler et al., 2012). Unfortunately, CYP450 metabolism is not always so straightforward, as is the case with prodrugs. CYP2D6 is responsible for the conversion of codeine, a prodrug with low binding affinity and efficacy at the mu-opioid receptor, into the more active metabolite morphine (Trescot, Datta, Lee, & Hansen, 2008). Poor metabolizers of CYP2D6 would have higher serum levels of codeine and lower serum levels of the more potent and efficacious metabolite morphine, which manifests as a reduction in analgesia (Crews et al., 2014). More importantly, rapid metabolizers of codeine have elevated levels of morphine and are at risk for respiratory depression (Gasche et al., 2004).

GENES ASSOCIATED WITH TREATMENT RESPONSE

Sodium-Dependent Serotonin Transporter and Solute Carrier Family 6 Member 4 (SLC6A4)

The serotonin transporter (SERT) is encoded by the gene SLC6A4 and is responsible for serotonin reuptake (Ku-

zelova, Ptacek, & Macek, 2010). Selective serotonin reuptake inhibitors (SSRIs) act by blocking this protein and increasing the amount of extracellular serotonin. Two variations in this protein affect expression of SERT. These variations are found within the serotonin-transporter-linked polymorphic region (5-HTTLPR) and are often described in scientific literature as a short (S) variant (missing 44 nucleotides) or the long variant (L). This long variant can be further subdivided into the wild-type allele L(A), or the rare version L(G). Both the S and L(G) variants are associated with reduction in serotonin transporter expression and function in cell culture and patients (Hu et al., 2006; Willeit & Praschak-Rieder, 2010). Recent meta-analyses have found associations between these risk variants and a poorer response to SSRIs and increased risk of side effects (Kato & Serretti, 2010; Porcelli, Fabbri, & Serretti, 2012; Serretti, Kato, De Ronchi, & Kinoshita, 2007). More specifically, these data suggest that carriers of one risk variant exhibit an increased likelihood of adverse effects when taking SSRIs, whereas having two copies of either risk variant results in a decreased response and an increased risk of adverse effects. Recent evidence also suggests that these risk variants are associated with abnormal cortisol signaling, impaired stress response, and emotional resilience (Alexander et al., 2009; Duman & Canli, 2015; Stein, Campbell-Sills, & Gelernter, 2009; Taylor, Larson, & Lauby, 2014). Clinically, SLC6A4 variants could be useful in predicting the response to several SSRIs including citalopram, escitalopram, fluoxetine, fluvoxamine, paroxetine, and sertraline. Alternative therapies that do not predominately target the serotonin transporter (e.g., non-SSRI antidepressant agents) may be beneficial in patients with these risk variants.

As research into the heritability of psychiatric illness progresses, the hope is to bridge the gap between symptom presentation and genetic variability...

Melanocortin 4 Receptor (MC4R)

MC4R is expressed in various regions of the brain, including the hypothalamus, and has a central role in the regulation of satiety, body weight, and energy balance (Tschritter et al., 2011). More than 70 variations have been identified, and approximately one half of these variants result in partial or total loss of function, which may lead to hyperphagia, hyperinsulinemia, binge eating, food-seeking behavior, and excessive hunger (Cole et al., 2010). One variant within this gene (rs489693C→A) is associated with increased weight gain in response to treatment with second-generation antipsychotic agents (SGAs). In a study by Malhotra et al. (2012), patients with the wild-type C/C genotype gained an average of 2.8 kg on SGAs after 12 weeks of treatment, whereas carriers of a single risk allele gained 4 kg and patients with the A/A genotype gained 8.2 kg. Some SGAs have less pronounced effects on weight gain or other metabolic indices (e.g., insulin resistance, dyslipidemia, hyperglycemia), and these lower risk SGAs (e.g., ziprasidone, lurasidone) may be more reasonable options in patients with the A/A risk genotype (Newcomer, 2005).

Glutamate Ionotropic Receptor Kainate Type Subunit 1 (GRIK1)

Kainate receptors (KAR) are ligand-gated ion channels that allow sodium and potassium into the cell upon glutamate binding (Ferrer-Montiel & Montal, 1996; Huettner, 2003). They are involved in cell depolarization, neuronal firing, and are likely involved in short- and long-term potentiation (i.e., neuronal plasticity) (Lerma, 2003). The GRIK1 gene encodes a subunit of the KAR, GluK1 (also known as GluR5 prior to 2009), and a SNP in this gene (rs2832407A→C) is associated with improved response to topiramate in the treatment of alcohol dependence (Kranzler, Covault, et al., 2014). Topiramate has been shown to directly inhibit kainate-induced currents in hippocampal neurons and recent evidence suggests it acts directly on the GluK1 (or GluR5) subunit (Gryder & Rogawski, 2003; Kaminski, Banerjee, & Rogawski, 2004; Meldrum & Rogawski, 2007). A study by Kranzler, Wetherill, et al. (2014) found that patients homozygous for the C allele had fewer heavy drinking days when compared to placebo and increased frequency of abstinent days when compared to A allele carriers when given 200 mg of topiramate per day. A follow-up study of these patients observed an extended benefit (3 to 6 months) in patients homozygous for the C allele after cessation of topiramate treatment (Kranzler, Wetherill, et al., 2014).

Human Leukocyte Antigen Class 1 (HLA-1)

The HLA-1 class of genes includes HLA-A, HLA-B, and HLA-C and encodes the heavy chains of class I antigen-presenting molecules that are expressed on most nucleated cells. These genes are highly polymorphic and code for proteins that bind and

present antigens to immune cells (Choo, 2007). Specific polymorphisms in this gene have been shown to affect response to the anti-epileptic carbamazepine (Tangamornsuksan, Chaiyakunapruk, Somkrua, Lohitnavy, & Tassaneeyakul, 2013). The variant HLA-B*1502 is associated with risk of developing Stevens-Johnson syndrome (SJS) and toxic epidermal necrolysis (TEN), predominately in patients of Asian descent. SJS and TEN are life-threatening conditions characterized by widespread lesions on the epidermis. Due to the severity of carbamazepine-induced SJS/TEN, the FDA has made label changes to this drug, in addition to suggesting genetic screening for patients of Asian ancestry before initiation of carbamazepine therapy (Ferrell & McLeod, 2008).

SUMMARY

The genes covered in the current review are involved in a number of psychiatric disorders and response to pharmacological agents. The COMT gene is involved in executive function and response to dopaminergic stimulants/COMT inhibitors. The Met/Met genotype, in particular, has been associated with anxiety-related disorders. The CACNA1C A allele has been linked to numerous mood lability disorders, including schizophrenia, bipolar disorder, and major depressive disorder. The –141 DEL variant of DRD2 is associated with substance abuse disorders and plays a significant role in the response to antipsychotic medications. Alterations in ABCB1 or CYP450 genes may result in abnormal drug absorption and metabolism, respectively, which directly affects serum levels of pharmacological agents. Lastly, risk variants in SLC6A4, MC4R, and HLA-1 are implicated in poor treatment response and/or adverse effects to SSRIs, second-generation antipsychotic agents, and carbamazepine, respectively, whereas patients homozygous for the C allele in GRIK1 are more likely to respond to topiramate for the treatment of alcohol abuse.

Psychiatric disorders and treatment response are largely multifactorial and not amenable to a simple solution or cure (Gottesman & Gould, 2003; Tsuang, Bar, Stone, & Faraone, 2004). In addition to genetic variability, environmental factors can also have a large impact on disease progression and these factors interact to make treatment even more complex (Manuck & McCaffery, 2014; Rutter, 2005). As research into the heritability of psychiatric illness progresses, the hope is to bridge the gap between symptom presentation and genetic variability by isolating additional genetic risk factors for individual disease states and medication response. Identifying haplotypes (i.e., a set of DNA variations, or polymorphisms, that tend to be inherited together), may help better explain the variability patients have in developing disorders and in their response to treatment. As the understanding of the mechanistic consequences of mutations in DNA increases, the ability to predict the agents most likely to be safe and efficacious for patients with mental health disorders will also increase.

Although the discipline of pharmacogenetics can be daunting at first glance, there are several commercial tests available that are designed to make this effort more manageable. With a simple buccal swab, any provider with prescriptive authority can get access to dozens of genetic biomarkers that can influence drug response. This is particularly welcome technology in the field of mental health, where there has been a dearth of actionable biomarkers. The ability to estimate metabolism rates or side effect risk prior to initiating therapy could be a valuable tool for prescribers. In addition, these tests can validate a history of treatment failure or help in identifying root causes of failure. In a time where everything in society is becoming more personalized, it stands to reason that health care should also be tailored to the individual. Pharmacogenetic testing is one step toward that goal.

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Dr. Amato is Medical Science Liaison, Mr. Boland is Clinical Research and Development Lead, Dr. Myer is Director, Clinical Research and Development, Dr. Few is Medical Science Liaison, and Dr. Dowd is Vice President of Medical Affairs, Genomind, Inc., King of Prussia, Pennsylvania.

All authors are employees of Genomind, Inc.

Disclaimer: The following drugs have not been approved by the U.S. Food and Drug Administration for use in some psychiatric conditions mentioned in the current article: tolcapone, verapamil, isradipine, nimodipine, pregabalin, gabapentin, and topiramate.

Address correspondence to Russell J. Amato, PhD, Medical Science Liaison, 2200 Renaissance Boulevard, Suite 100, King of Prussia, PA 19406-2755; e-mail: ramato@genomind.com.

Received: June 22, 2017

Accepted: August 14, 2017

doi:10.3928/02793695-20170928-01