Using Pharmacogenetics and Advanced Neuroscience to Personalize Treatment of Psychiatric Illness

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In any given year, 26.2% of individuals in the United States experience a diagnosable psychiatric illness [National Institute of Mental Health. 2012]. Approximately 6% of adults suffer from a seriously debilitating mental illness. Among adolescents aged 13 to 18 years, 46.3% experience symptoms of psychiatric illness, and 21.4% experience a severe disorder. In this presentation, Laura G. Leahy, DrNP(c), APRN, APNSolutions, LLC, Sewell, New Jersey, USA, presented real-life prescriptive challenges in treating patients with psychiatric illnesses and offered innovative ways to address them. She discussed clinical tools for personalizing psychopharmacologic treatment, including psychopharmacogenetics, laboratory studies, review of systems, symptom evaluation, and observation.

Official Peer-Reviewed Highlights From

American Psychiatric Nurses Association

CASE STUDY AND PERSONALIZED TREATMENT

Ms Leahy presented the case of a boy, aged 8 years, with symptoms of restlessness, fidgeting, inattention, poor sleep, limited appetite, forgetfulness, frustration, and decreasing grades. He was diagnosed with attention-deficit/hyperactivity disorder (ADHD) and was prescribed an extended-release psychostimulant by his pediatrician. The restlessness and fidgeting initially improved, but the patient developed an upset stomach and headaches, and his grades continued to decrease. The psychostimulant was discontinued, and the physical and behavioral symptoms continued. Results of a full medical workup and computed tomography scan of the brain were normal, so he was referred to a psychiatric mental health nurse practitioner (PMHNP), who started him on a trial of the selective norepinephrine reuptake inhibitor (SNRI) atomoxetine.

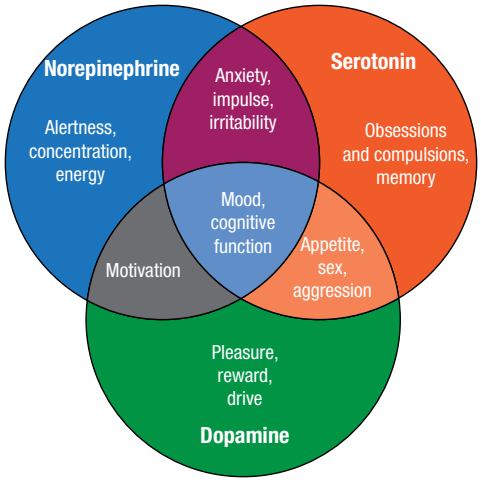
Many factors influence the development of psychiatric illness, including genetic, epigenetic, developmental, and environmental factors. These factors should be considered when evaluating and treating patients.

According to Ms Leahy, the use of observation, education, clinical testing, and nursing experience leads to improved decision making and patient outcomes. A complete evaluation includes a review of systems and laboratory studies, including complete blood count, electrolytes and metabolic panel, and hormone and vitamin-level testing. Neurotransmitter levels are also important, as they affect mood and mental function (Figure 1).

Norepinephrine and dopamine deficiencies are associated with ADHD. A deficiency of norepinephrine contributes to inattention and elevated anxiety responses. Dopamine deficiency is associated with poor concentration, inattention, and inability to regulate inhibitions.

The case study patient stayed on atomoxetine, and his symptoms were in remission through middle school. However, by age 14, he was missing occasional doses of atomoxetine and developed symptoms of agitation, irritability, defiance, and sleep fluctuations from hypersomnolence to insomnia. Family therapy was started, but after 3 months, his symptoms worsened. A review of the family history revealed that the patient's paternal grandfather suffered from manic depression and alcoholism and his paternal uncle committed suicide in his mid-20s. Pharmacogenetic testing, via the Genecept salivary assay ordered by the PMHNP, revealed that the patient had the following gene variants: 5-HT_{2C} C/C, $CACNA_{1C}$ G/A, COMT Val/Val, MTHFR C/T, and CYP2D6 IM/PM. The implications of these gene variants and others associated with psychiatric illness are shown in Table 1.

Figure 1. Effects of Neurotransmitters



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Adapted from Healy D et al. The enhancement of social functioning as a therapeutic principle in the management of depression. *J Psychopharmacol.* 1997;11:S25-S31. With permission from British Association for Psychopharmacology.

On the basis of his genotype, the patient was prescribed lithium and L-methylfolate. From ages 19 to 21, the patient abruptly discontinued all of his medications. He began drinking on weekends and weeknights and smoking marijuana to "help him sleep." When drinking, he became angry and aggressive. After failing his first year of college and getting arrested for driving under the influence, he agreed to return to the PMHNP. Because the patient hated the blood draws necessary with lithium, the PMHNP started a trial of gabapentin, which was consistent with his genotype. Recent studies demonstrated the efficacy of gabapentin for alcohol and marijuana abstinence and as a sleep aid.

PSYCHOPHARMACOLOGY

Personalized pharmacologic treatment of psychiatric illness involves selecting therapies based on a patient's history, clinical features, laboratory and other studies, genotype, and potential adverse effects of medications. Approximately 50% to 60% of patients benefit from their first medication trial; 30% to 50% benefit from their second medication trial [Trivedi MH et al. *Am J Psychiatry.* 2006]. Approximately 25% to 33% of patients do not respond after >3 trials with adequate medication and are considered treatment resistant.

Many psychotropics are associated with significant adverse effects, such as an increased risk of mortality in elderly patients with dementia using atypical antipsychotics [US Food and Drug Administration.

Table 1. Genotypes and Implications for Personalized Medicine

Genotype	Implications
5-HT_{2C} C/C [Zhang JP, Malhotra AK. *Expert Opin Drug Metab Toxicol.* 2011]	Satiety signaling activity Variants may increase risk of weight gain and metabolic syndrome when taken with psychotropics Use caution with atypical antipsychotics
$CACNA_{1C}$ G/A [Ferreira MAR et al. *Nat Genet.* 2008]	Regulates calcium influx along cell membrane Variants may increase excitatory neurotransmission, risk of depression, bipolar disorder, and schizophrenia Lithium may stabilize mood, relieve agitation and irritability, improve sleep May also use atypical antipsychotics, anticonvulsant mood stabilizers
COMT Val/Val [Zhang JP, Malhotra AK. *Expert Opin Drug Metab Toxicol.* 2011]	Regulates dopamine and norepinephrine in prefrontal cortex Impacts memory, attention, judgment Variants may be associated with poor executive function, risk for substance abuse Psychostimulants, bupropion, atomoxetine, and wake-promoting agents may be effective
MTHFR C/T [Robinson DS. *Primary Psychiatry.* 2009]	Conversion of folic acid to its most active form Reinforces treatment resistance and psychiatric symptoms Variants may decrease ability to regulate movement of monoamines across synapse, increase risk for depression, bipolar disorder, schizophrenia, and autism L-methylfolate added to regimen may be effective
CYP450 enzyme 2D6 IM/PM, 2C19, 3A4, 3A5 [Zhang JP, Malhotra AK. *Expert Opin Drug Metab Toxicol. 2011;* Weizman S et al. *Neuropsychopharmacol Hung.* 2012]	Enzymes involved in hepatic metabolism of psychotropic and other drugs Variants associated with adverse drug effects, lack of response to multiple therapies Dose adjustments necessary for drugs that are substrates of these enzymes
DRD2 [Zhang JP, Malhotra AK. *Expert Opin Drug Metab Toxicol.* 2011]	Aids in regulation of movement and perception Variant may increase risk for adverse drug effects, decrease response to atypical antipsychotics Nonantipsychotic mood stabilizers may be effective
$SLC6A_4$ [Weizman S et al. *Neuropsychopharmacol Hung.* 2012]	Presynaptic serotonin reuptake Variants may increase cortisol burden, decrease response to SSRIs, increase risk for treatment-resistant depression or PTSD Non-SSRI antidepressants Caution initiating and discontinuing SSRIs
ANK_3 [Ferreira MAR et al. *Nat Genet.* 2008]	Stabilizes sodium channels and excitatory neurotransmission Variants may decrease sustained attention, increase risk for bipolar disorder, schizophrenia, cyclical mood disorder Anticonvulsant mood stabilizers, psychostimulants, wake-promoting agents may be effective

5-HT_{2C} (C/C), 5-hydroxytryptamine (serotonin) receptor 2C, C/C variant; ANK_3, ankyrin G; $CACNA_{1C}$ G/A, calcium channel, voltage-dependent, L type, alpha 1C subunit G/A variant; COMT Val/Val, catechol-O-methyltransferase Val/Val variant; MTHFR C/T, methylenetetrahydrofolate reductase C/T variant; PTSD, posttraumatic stress disorder; $SLC6A_4$, solute carrier family 6 (serotonin transporter) member 4; SSRI, selective serotonin reuptake inhibitor.

http://www.fda.gov/Drugs/DrugSafety/PostmarketDrugSafetyInformationforPatientsandProviders/ucm124830.htm. Accessed December 24, 2014]; increased suicidality in children, adolescents, and young adults using antidepressants [US Food and Drug Administration. http://www.fda.gov/Drugs/DrugSafety/InformationbyDrugClass/UCM096273. Accessed December 24, 2014]; and a risk of sudden death and cardiovascular events and potential for abuse and dependence with psychostimulants [US Food and Drug Administration. http://www.fda.gov/Drugs/DrugSafety/ucm277770.htm. Accessed December 24, 2014]. Atomoxetine, duloxetine, nefazodone, and pemoline have the potential to cause severe hepatotoxicity [United States Food and Drug Administration. *MedWatch Safety Alerts for Human Medical Products.* 2005]. Care must be taken when treating women of childbearing age, as most of the therapies are not approved for use in pregnancy and may have teratogenic effects. However, serotonin selective reuptake inhibitors (SSRIs) have been used successfully during pregnancy. Most medications are not approved for children, but many have a long successful history of use in children. The dose of and duration on medication should be maximized in children who have some response. With elderly patients, a thorough medical and medication history should be taken. Doses may need to be lowered due to slower liver metabolism, and adverse effects should be closely monitored.

Treatment options include combination and augmentation strategies, such as lithium, triiodothyronine, and stimulants; atypical antipsychotic agents; omega-3 fatty acids and L-methylfolate; modafinil and stimulants; and lamotrigine. Patients with treatment-resistant symptoms may be switched between an SSRI and an SNRI (symptoms: alteration in concentration, energy, fatigue, anxiety, impulsivity, memory, or irritability); an SSRI and a norepinephrine-dopamine reuptake inhibitor (NDRI; symptoms: alteration in motivation, pleasure, aggression, sexual dysfunction, weight, memory, or obsessions and compulsions); or an SNRI and an NDRI (symptoms: alteration in energy, alertness, concentration, attention, pleasure, or motivation). Table 2 lists the drug classes used for psychiatric illnesses and their key features.

Ms Leahy concluded that the holistic approach to treatment of patients with psychiatric symptoms helps to identify potential medical mimics and other nonpsychiatric conditions. Moving into the 21st century, PMHNPs must integrate their powers of observation with concepts of advanced neuroscience, brain chemistry and pathology, and pharmacogenetics and partner with their patients to develop a "tool kit" to improve their quality of life.

Table 2. Drug Classes and Key Features

Drug Class	Key Features
Psychostimulants	
Methylphenidate Dexmethylphenidate Mixed amphetamine salts Amphetamines Alpha 2 adrenergic agents	Act on prefrontal cortex, affecting executive functioning Enhance dopamine and norepinephrine First-line therapy for ADHD No adverse effect on growth and development Safe and effective in age 3 y to adults
Nonstimulants	
Atomoxetine	SNRI Effective for inattention with anxiety Reduced potential for abuse
Clonidine	Short acting used for sedation Reduces aggression and impulsivity associated with ADHD
Guanficine	Short acting, less sedating, and better tolerated than clonidine Long acting helpful for impulsivity and hyperactivity
Antidepressants	
SSRI SNRI TCA MAOI Atypical agents	Each class associated with a 60% to 80% response rate Symptom improvement may begin as early as 1 to 2 wk Full benefits may not be evident for 6 to 8 wk TCAs are potentially lethal with overdose due to cardiac effects MAOIs used for TRD
Anxiolytics	
Benzodiazepines Buspirone Antihistamines Gabaminergic agents	Benzodiazepines most useful for anxiety and withdrawal syndromes but have potential for dependence and addiction Antidepressants useful for chronic anxiety Propranolol and clonidine useful for panic and performance anxiety Antihistamines useful for anxiety with comorbid insomnia
Mood stabilizers	
Lithium Anticonvulsants	Combinations may be more effective for response and remission Patients often enjoy mania and hypomania and may not adhere to medication regimen Lamotrigine may be more effective for TRD and bipolar depression than manic or hypomanic states; potential risk of Stephen's Johnson syndrome
Antipsychotics	
First generation Second generation Third generation	First generation has greater risk of dystonia and other adverse effects but may be more effective in crisis First generation has high affinity for dopamine receptors Second and third generations have greater impact on negative symptoms of psychosis with fewer adverse effects Second and third generations antagonize both dopamine and serotonin receptors To switch, cross titrate the agents until the first drug has been discontinued and the second drug reaches a therapeutic dose

ADHD, attention-deficit/hyperactivity disorder; MAOI, monoamine oxidase inhibitor; SNRI, selective norepinephrine reuptake inhibitor; SSRI, selective serotonin reuptake inhibitor; TCA, tricyclic antidepressant; TRD, treatment resistant depression.