New Biologic Tools in Psychiatry

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By Adriana Foster, MD [1]

The psychiatric community has a need for diagnostic and predictive tests. Some recent techniques have just become available for clinical care.

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The psychiatric community, our patients, and patient advocates have long had a great desire and need for diagnostic and predictive tests. As practitioners, we have to admit time and time again to patients and families that we “cannot measure the serotonin level in the brain” and “cannot diagnose schizophrenia with a brain MRI.” Our limitations are in contrast to other areas of medicine, in which diagnostic and prognostic tests are more readily available. In psychiatry we have a rather well-developed battery of screening and structured clinical diagnostic tools as well as symptom rating scales. However, attempts to include testing of biologic markers in the diagnosis of mental illness have come and gone (eg, dexamethasone suppression test for the diagnosis of depression, plasma homovanillic acid measurement to predict antipsychotic response in schizophrenia).

This article summarizes new developments in pharmacogenetics, therapeutic drug monitoring, diagnostic tests, and compliance assessment tools. Some of these techniques have just crossed the road from research to clinical care. They reflect the widespread advances in neurobiology and technology and should be followed by even greater progress in the next decade. However, clinicians are generally skeptical of “gee-whiz” tests and payers are usually even more concerned. The verdict of psychiatric researchers and clinicians will determine whether they will become part of day-to-day psychiatric practice.

Case vignettes

Parkinsonism developed in a middle-aged woman with psychosis and no known medical problems while she was taking risperidone. When her regimen was switched to aripiprazole, excessive sedation developed. Both reactions occurred at average recommended doses.

Psychomotor hyperactivity developed in a 30-year-old man with depression who was taking sertraline. When his regimen was changed to citalopram, a seizure-like episode developed. He had no history of seizures and never had a seizure after citalopram was discontinued.

GENETICS

AmpliChip P450

Our understanding of treatment for mental illness, including cases like these, is broadening with the findings of pharmacogenetics and pharmacogenomics. In years to come, we may have the ability to write individualized prescriptions after testing our patients for vulnerability to limiting side effects such as weight gain and agranulocytosis and for their potential response to certain drugs.1,2 The first step toward personalized medicine is now available with FDA approval of Roche's AmpliChip CYP450. This tool allows clinicians to obtain the analysis of cytochrome (CYP) 2D6 and 2C19 polymorphisms and to understand the metabolic rate of these 2 important liver enzymes in an individual. Thus, clinicians can adopt a personalized and predictive approach to prevent adverse drug reactions and to optimize the dose of medications prescribed.

The response to drugs is potentially influenced by factors such as age, gender, ethnicity, concomitant disease, liver and kidney function, diet, smoking, pregnancy, and drug-drug interactions. In addition, inherited variations in the DNA sequence of the genes responsible for drug-metabolizing enzymes, drug receptors, transporters, and signal transducers are believed to have significant effects on the efficacy and toxicity of drugs. Predicting polymorphisms in drug-metabolizing enzymes and serotonin, dopamine, and norepinephrine system receptors and transporters could increase the effectiveness of prescribing drugs, reduce the time to drug response,
avoid potential side effects, and lower the overall cost of mental health treatment.\textsuperscript{3,4} A recognized example outside the psychiatric field is the influence of CYP-450 2C9 polymorphism on response to warfarin. The risk of bleeding can vary widely with the 2C9 genotype between poor metabolizers and patients with the normal allele.\textsuperscript{5}

The microsomal CYP-450 enzymes are responsible for approximately 80\% of the oxidative drug metabolism and 50\% of the elimination of commonly prescribed drugs.\textsuperscript{5} CYP 2D6 metabolizes approximately 25\% of drugs biotransformed by CYPs and contributes to the metabolism of many psychotropic drugs, including antipsychotics (haloperidol, thioridazine, perphenazine, chlorpromazine, risperidone,\textsuperscript{7} and aripiprazole) and antidepressants (amitriptyline, nortriptyline, clomipramine, desipramine, imipramine, paroxetine, fluvoxamine, fluoxetine, venlafaxine, and duloxetine) as well as other psychiatric drugs.\textsuperscript{8,9} CYP 2D6 is encoded by a gene located in chromosome 22 and has a high level of genetic polymorphism, including mutations, deletions, and duplications. There are more than 50 variants of CYP 2D6, resulting in 4 phenotypes, all of which have ethnic variability (Table 1).\textsuperscript{10}

The gene encoding CYP 2C19 also has significant genetic variability. This enzyme metabolizes psychotropics such as amitriptyline, clomipramine, citalopram, escitalopram, sertraline, and diazepam: 2\% to 4\% of whites, 10\% to 25\% of East Asians, 1\% to 5\% of African Americans, 2\% of North Africans and Middle Easterners, and 4\% of Mexican Americans are poor metabolizers.\textsuperscript{8,10}

In a study of patients in a state hospital who discontinued treatment with a common antipsychotic, 9\% of those genetically tested were poor metabolizers of the drug, 38\% were taking medications that inhibit drug metabolism, and the remaining 53\% had side effects due to unknown causes.\textsuperscript{11} There are limited but compelling data showing that the cost of treating patients with extremes of CYP 2D6 (poor and ultrarapid metabolizers) is significantly higher than that of treating patients who are intermediate and extensive metabolizers.\textsuperscript{12}

In 2005, the FDA cleared the AmpliChip CYP450 tool, which uses microarray technology to determine the 2D6 and 2C19 genotype from genomic DNA and allows for the stratification of patients into the 4 categories of biometabolism. Ideally, genotyping of patients should occur before treatment with psychotropic drugs in order to identify the individuals likely to experience side effects or have poor response to recommended doses of certain drugs. However, it is not yet clear whether the use of CYP-450 genotyping will prove to be cost-effective. Currently, there are no guidelines for when this test should be performed, although there are data that seem to indicate that poor metabolizer status correlates with significant side effects from the psychotropics metabolized by CYP2D6 and 2C19.\textsuperscript{11}

The test is performed by molecular diagnostic laboratories using AmpliChip technology and requires about 4 mL of blood from the patient (see Table 2 for a list of laboratories offering this test).

### Table 2 Summary of new tests in psychiatry

<table>
<thead>
<tr>
<th>Test</th>
<th>Use</th>
<th>Company</th>
<th>Status</th>
</tr>
</thead>
<tbody>
<tr>
<td>AmpliChip CYP450</td>
<td>Analysis of polymorphisms in CYP-450 2D6 and 2C19</td>
<td>Roche Diagnostics Laboratories performing the test with Roche platform: Georgia Esoteric and Molecular Lab, LLC (gamoleculararlab.com) LabCorp (labcorp.co)</td>
<td>FDA cleared</td>
</tr>
</tbody>
</table>
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<table>
<thead>
<tr>
<th><strong>InstaRead Lithium System</strong></th>
<th>In-office testing of lithium levels</th>
<th>ReliaLAB (relialab.com)</th>
<th>FDA cleared</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>NeuroLex Indicator Report Service</strong></td>
<td>Quantitative electroencephalogram used as aid to clinical assessment in ADHD diagnosis</td>
<td>Lexicor (lexicor.com)</td>
<td>Filed for 510(k) FDA clearance</td>
</tr>
<tr>
<td><strong>Medication Event Monitoring System (MEMS)</strong></td>
<td>Electronic monitoring of patient compliance</td>
<td>Aardex, Ltd (aardex.ch)</td>
<td>NA</td>
</tr>
<tr>
<td><strong>Hair analysis</strong></td>
<td>Detection of substance use: amphetamine, cannabis, cocaine, MDMA, MDEA, opiates, phencyclidine detection</td>
<td>Psychedica Corporation (psychedica.com)</td>
<td>FDA cleared</td>
</tr>
</tbody>
</table>

ADHD, attention-deficit/hyperactivity disorder; MDMA, 3,4 methylenedioxymethamphetamine (Ecstasy); MDEA, 3,4-methylenedioxy-N-ethylamphetamine; NA, not available.

**THERAPEUTIC DRUG MONITORING**

**InstaRead Lithium System: point-of-care test for lithium levels**

Through future advances in pharmacogenetics, we may be able to predict a patient's response to
lithium. In current clinical practice, however, we need to optimize monitoring of lithium treatment so that we can prescribe it in a safe manner. Lithium is FDA approved for treatment of mania in patients with bipolar disorder.

**Case vignette**

A man with schizoaffective disorder, who stopped taking valproic acid before the current episode, was given lithium without improvement in manic symptoms. The psychiatrist to whom he was referred after lithium was started ordered measurement of serum lithium to determine whether an increase in dosage was necessary. The patient's level was 2.3 mEq/L and he showed no clinical signs of lithium toxicity. The only concomitant medication was losartan/hydrochlorothiazide. Lithium was stopped and serial levels decreased to less than 1 mEq/L in 5 days. The patient's serum creatinine level and urinary creatinine clearance were within normal range.

The therapeutic range of lithium is narrow (0.6 to 1.2 mEq/mL) and overdose can quickly lead to CNS toxicity and renal failure requiring dialysis. Multiple drug interactions are possible: angiotensin-converting enzyme inhibitors, angiotensin receptor antagonists, cyclooxygenase-2 inhibitors, NSAIDs, loop diuretics, carbonic anhydrase inhibitors, thiazide diuretics, and tetracyclines may increase lithium levels. Caffeine (xanthine derivatives), bicarbonate and/or a high-sodium diet, theophylline, and urea may lower lithium serum concentrations. Laboratory blood testing is absolutely required and can be a burden for patients who otherwise would greatly benefit from lithium treatment.

ReliaLAB's InstaRead Lithium System is now FDA approved and the Clinical Laboratory Improvement Amendment is waived for testing plasma lithium levels in-office. The method involves a blood sample obtained by finger stick and analyzed in a processor through a colorimetric assay. The test must be performed 12 hours after the last lithium dose; results are available in 5 minutes. If results are abnormal, the test must be repeated in 5 minutes. Any office staff member designated by a physician can perform the test. The results are within 0.2 mEq/mL of the results obtained through a clinical laboratory. The test is sensitive to 0.1 mEq/L of lithium and linear between 0.1 and 2.5 mEq/L.

Having an office-based, point-of-care lithium testing system ensures rapid access to results for clinicians and can avoid patient burden and delay in clinical decisions critical to patient safety. This test can increase the overall quality of care by adding convenience for the patient, thus encouraging compliance. However, there are no inoffice alternatives for testing renal and thyroid function, so physicians will still have to have their patients visit a laboratory periodically in order to monitor these parameters. Another in-office system for detection of suppressed white blood cell levels and absolute neutrophil cell levels for use in patients taking clozapine is under development by ReliaLAB.

**DIAGNOSTIC TOOLS**

**NeuroLex Indicator Report Service for ADHD assessment**

Electroencephalographic (EEG) changes in children with attentiondeficit/hyperactivity disorder (ADHD) have been studied extensively. These studies document a higher percentage of slow theta waves, associated with inattention and lower percentage of beta waves, associated with focus and attention, in children with ADHD versus controls, as summarized by di Michele and colleagues. The ratio of theta to beta waves can be measured with quantitative EEG (QEEG) and has been referred to as an attention index. Monastra and colleagues showed that 90% of children with ADHD that were diagnosed with clinical tools, including DSM-IV criteria, parent and teacher ADHD rating scales, and continuous performance tests (CPT), had scores above the average cutoff for age on the QEEG attention index, and 94% of children without ADHD did not.

Based on this finding, Lexicor developed a QEEG method, the NeuroLex Indicator Report Service, intended to be used by physicians as an aid in clinical evaluation for ADHD, in addition to a clinical interview, parent and teacher rating scales, and CPT. The system includes collection of digital EEG data that are transmitted securely via the Internet to Lexicor from the physician’s office. The patient's information is assessed and compared with age-specific normative databases and a report is issued to the physician in a graph format. The procedure is noninvasive, QEEG is collected in a resting condition, and it takes approximately 1 hour to complete. Lexicor has a 510(k) submission pending FDA review to qualify the Neurolex EEG analysis service as an aid in the DSM-IV-based assessment of ADHD. Replication of findings of Monastra and colleagues by other investigators,
including a structured clinical interview to rule out other psychiatric disorders in the ADHD and control groups, is needed to further support differentiation of ADHD from a control group based on QEEG.

As reported by Clarke and colleagues²⁰ and summarized by di Michele and colleagues¹⁷ QEEG can also differentiate between subtypes of ADHD. There are reports showing electrophysiologic characteristics in various psychiatric illnesses.²¹-²³ For example, lateralization of cerebral activity on QEEG in opposite hemispheres has been associated with opposite mood states in bipolar disorder, and another report shows that QEEG can discriminate between dementia and depression. Lastly, it has been proved that depressed patients with higher pretreatment central activity on QEEG are more likely to benefit from electroconvulsive therapy. However, specific QEEG patterns are not yet determined for all psychiatric disorders, including bipolar disorder, major depressive disorder, anxiety disorders, and conduct disorder. Thus, we do not know whether QEEG has the potential to differentiate between ADHD and other childhood disorders and how comorbidity of ADHD with such illnesses will influence the QEEG pattern. In a longitudinal study, Monastra²⁴ found that using QEEG and a neuropsychological test of attention for DSM-IV-based assessment for ADHD and the education of parents about ADHD implications helped families with children affected by ADHD comply with medical recommendations. There is no information to date about the cost-effectiveness of adding this QEEG test to the clinical evaluation battery used for ADHD diagnosis.

**COMPLIANCE**

**MEMS system for electronic monitoring of patient compliance**

Treating chronic and severe mental illness is a considerable challenge. Obstacles can be related to illness itself (paranoid ideation, depression, amotivation, poor insight, and substance abuse) or to treatment (adverse effects, misunderstanding, and false expectations of medication effects).²⁵ Compliance with medication helps prevent symptom relapse and fosters patient stability.²⁶ In addition, some antipsychotics and valproate have been shown to have neuroprotective effects.²⁷,²⁸ Physicians have a major role in ensuring medication adherence. In addition to maintaining a good therapeutic relationship and evaluating compliance clinically, a method currently used in clinical studies--the Medication Event Monitoring System (MEMS)--is available to aid physicians in their assessment of patient adherence. Byerly and colleagues²⁹ showed that physicians greatly overestimate patient compliance by clinical assessment when compared with an electronic monitoring system such as MEMS. Clearly, documentation provided by an electronic monitoring system (the date and time of bottle opening) does not ensure that the patient actually ingested the prescribed medication. However, in Byerly's study of 25 psychotic patients, MEMS detected nonadherence in 12 patients, whereas clinical assessment failed to detect noncompliance in any of the 25 participants. MEMS incorporates microcircuitry into drug packaging, which is able to sense the maneuvers used to remove a dose of drug. This information is stored in the memory with the time and date and can be communicated to a computer database from which reports can be displayed and printed.

**Hair analysis for drug testing**

The hair analysis by radioimmunoassay (RIA) is emerging as a clinically effective way for detection of illicit drugs. The combination of self-reporting, urine analysis, and hair analysis has a high sensitivity for illicit drug detection. Swartz and colleagues³⁰ found that of 203 patients with schizophrenia, only 16.3%; self reported illicit drug use and only 12.4% had a positive urine test, but 31% had a positive hair analysis by RIA. Self-report, urine test, and hair analysis in combination yielded a 38.4% detection rate. Tolerability of hair analysis needs to be further studied, although in this group of patients only 10% refused the analysis. Hair analysis can detect illicit drug exposure from 2 to 3 days after initial use, to any time thereafter, depending on the length of the hair sample. A hair sample of 1.5 inches detects use in the previous 90 days. Substances for which hair is commonly tested are amphetamines, cocaine, cannabis, opiates, and phencyclidine. Compared with urine testing, the likelihood of tampering is reduced because the hair sample is collected directly from the patient. The Clinical Antipsychotic Trials of Intervention Effectiveness (CATIE), a landmark study of treatment in schizophrenia, incorporated the RIA of hair and urine drug tests in the substance abuse assessment performed at enrollment.³¹ The study detected substance use in 60% of the 1460
patients with schizophrenia and evidence of 37% current substance use disorder, similar to the findings in the study by Swartz and colleagues. It is noteworthy that the findings about alcohol use in this study were obtained only from self-report during the clinical assessments and not measured by any laboratory studies.

The drawbacks of hair analysis include the possibility of false-positives for cannabis on RIA (although, according to the Psychemedics Web site, all positive results obtained with RIA are automatically followed by analysis by gas chromatography); the inability to test for alcohol, benzodiazepines, or barbiturates; and the high cost of RIA. However, in addition to its medical and legal uses, hair analysis may find a place in clinical practice, especially with patients who have severe mental illnesses such as bipolar disorder or schizophrenia, in which the high comorbidity with substance abuse can particularly limit the response to treatment.

### SUMMARY

A variety of tests are used in the research setting, some have a role in clinical practice and others may be used in the clinic at some future time (Table 3). Genetic testing for CYP-450 enzymes with the AmpliChip is starting to penetrate clinical research, and guidelines will be elaborated soon to help clinicians in its use. The other tools are in earlier stages of clinical application. Time will tell whether these tools can prove their effectiveness and diagnostic specificity. In addition, they will have to become cost-effective to gain payer support. If these tools prove to advance our ability to diagnose and treat mental illness, our role will extend to educating the patients, the public, and the service planners about them.

<table>
<thead>
<tr>
<th>Test</th>
<th>Pros</th>
<th>Cons</th>
</tr>
</thead>
<tbody>
<tr>
<td>Structural imaging CT, MRI of brain</td>
<td>Can be helpful in:</td>
<td>Patterns of abnormality have been described in schizophrenia,</td>
</tr>
<tr>
<td></td>
<td>• Dementia</td>
<td>bipolar disorder, depressive disorders, and anxiety</td>
</tr>
<tr>
<td></td>
<td>• Brain injury</td>
<td></td>
</tr>
<tr>
<td></td>
<td>• Cerebrovascular etiology of mood symptoms</td>
<td></td>
</tr>
<tr>
<td></td>
<td>• Ruling out brain tumors or infections</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Organic with use at first-episode psychosis or mania</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Optional for ECT work-up&lt;sup&gt;33,34&lt;/sup&gt;</td>
<td>MRI is expensive</td>
</tr>
<tr>
<td></td>
<td>CT is relatively inexpensive</td>
<td>Patients with claustrophobia cannot tolerate MRI</td>
</tr>
<tr>
<td>Functional imaging PET, SPECT, fMRI</td>
<td>Differential diagnosis of dementia with specific patterns in:</td>
<td>No specificity in mood and psychotic disorders although</td>
</tr>
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<td></td>
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</tr>
</tbody>
</table>
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- Alzheimer disease
- Vascular dementia
- Pick disorder
- Frontotemporal dementia\(^{33,34}\)

**EEG**

Can be helpful in:
- Seizures
- Delirium
- Dementia

Not easily accessible, patient has to be still

**TSH**

Routine organic work up of mood and psychotic symptoms

Monitoring of thyroid function during:
- Lithium treatment
- Use of thyroid hormone for antidepressant augmentation

Unclear if TSH should be used routinely in every first episode psychiatric illness

**Therapeutic drug monitoring**

- Antidepressants: Amitriptyline, nortriptyline, desipramine levels: useful since therapeutic range is narrow
- Mood stabilizers: lithium requires close monitoring (see article text)
- Valporate levels for acute mania and maintenance bipolar disorder are emerging\(^{35}\)

Tricyclic antidepressants are no longer widely used by psychiatrists

Carbamazepine levels have no relevance for psychiatric therapeutic effect

New anticonvulsants do not allow levels

Antipsychotic levels are not frequently used as clinical tool and are
Role of therapeutic drug monitoring of olanzapine, risperidone, and clozapine is emerging.\(^{36,37}\)

ECT, electroconvulsive therapy; PET, positron emission tomography; SPECT, single photon emission computed tomography; fMRI, functional MRI; MDD, major depressive disorder; OCD, obsessive compulsive disorder; PTSD, posttraumatic stress disorder; EEG, electroencephalogram; TSH, thyrotropin.

Dr Foster is an assistant professor in the department of psychiatry and health behavior at the Medical College of Georgia in Augusta. Her clinical and research interests include schizophrenia and psychotic disorders, in particular treatment of refractory schizophrenia. She reports that she is a member of the Roche Diagnostics Psychiatry Advisory board and has received an educational grant from Astra-Zeneca. In addition, the Medical College of Georgia has received an educational grant from Roche Diagnostics for a CME activity, and their department of psychiatry and pathology has applied for research funding for translational research in psychiatry.

**Drugs Mentioned in This Article**

- Amitriptyline (Elavil, Endep)
- Aripiprazole (Abilify)
- Chlorpromazine (Largactil, Thorazine)
- Citalopram (Celexa)
- Clomipramine (Anafranil)
- Clozapine (Clozaril)
- Desipramine (Norpramin, Pertofrane)
- Diazepam (Valium)
- Duloxetine (Cymbalta)
- Escitalopram (Lexapro)
- Fluoxetine(Prozac)
- Fluvoxamine (Luvox)
- Haloperidol (Haldol)
- Imipramine (Tofranil)
- Lithium (Eskalith)
- Losartan/hydrochlorothiazide (Hyzaar)
- Nortriptyline (Aventyl, Pamelor)
- Paroxetine (Paxil)
- Perphenazine (Etrafon, Trilafon)
- Risperidone (Risperdal)
- Sertraline (Zoloft)
- Thioridazine (Mellaril)
- Valproate/Valproic acid (Depakon/Depakene)
- Venlafaxine (Effexor)
- Warfarin (Coumadin)

**References**

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27. Parikh V, Evans DR, Khan MM, Mahadik SP. Nerve growth factor in never-mediated first-episode
psychotic and medicated chronic schizophrenic patients: possible implications for treatment outcome. Schizophr Res. 2003;60:117-123.

Evidence-based References


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