



# Psychopharm R E V I E W

Volume 45 • Number 2 • February 2010

*Timely Reports in  
Psychopharmacology and  
Device-Based Therapies*

Philip G. Janicak, MD, Editor

Formerly Frank Ayd's International Drug Therapy Newsletter

## Toward Early, Personalized, Rational Polypharmacy In Psychiatry: A Tri-Dimensional Approach

Alexander B. Niculescu III, MD, PhD, and Leslie A. Hulvershorn, MD, MSc

### LEARNING OBJECTIVES

**After participating in this activity, the psychiatrist should be better able to:**

- Interpret the current dilemmas facing psychopharmacologists relative to the paucity of clinical studies that could inform evidence-based polypharmacy.
- Evaluate emerging advances in genetics and neuroscience to tailor treatment and polypharmacy regimens.
- Plan strategies to improve current treatment approaches and outcomes.

### CURRENT STATE OF TREATMENT

Psychiatry is a complex field of medicine in which a growing understanding of the underlying disease biology is not fully integrated into clinical practice. Diagnosis is based on subjective personal history and clinical criteria. The latter are chosen through a consensus process by committees of experts in the field, and encoded in the *Diagnostic and Statistical Manual of Mental Disorders (DSM)* and its international homologue, the International Classification of Diseases. These criteria are re-evaluated and updated periodically, on average every two decades, although the pace is likely to accelerate.<sup>1</sup> The lack

### IN THIS ISSUE

Toward Early, Personalized, Rational Polypharmacy in Psychiatry: A Tri-Dimensional Approach . . . . .	9
CME Quiz . . . . .	16

of objective diagnostic tests and empirical data-based approaches to psychiatric classification are possible reasons for the relative lack of reproducibility in psychiatric clinical trials.

Dr. Niculescu is Assistant Professor of Psychiatry and Medical Neuroscience, Indiana University School of Medicine, Indianapolis, IN, Staff Psychiatrist, Indianapolis VA Medical Center, Indianapolis, IN, and Director, INBRAIN and Laboratory of Neurophenomics, Institute of Psychiatric Research, 791 Union Drive, Indianapolis, IN 46202, E-mail: anicules@iupui.edu; and Dr. Hulvershorn is Clinical Instructor, NYU Child Study Center, New York University School of Medicine, New York, NY.

Dr. Niculescu has disclosed that he is/was the recipient of grant/research support from Eli Lilly and Asternad; is/was a member of the speakers bureau Pfizer and Janssen; and is/was a scientific co-founder of Mindscape Diagnostics. Dr. Hulvershorn has disclosed that she has no significant relationships with or financial interests in any commercial organizations pertaining to this educational activity.

Dr. Janicak has disclosed that he is/was the recipient of grant/research support from Otsuka and Neuronetics; is/was a consultant/advisor to Bristol-Meyers Squibb/Otsuka, Janssen, AstraZeneca, and Neuronetics; is/was a member of the speakers bureau of AstraZeneca, Bristol-Meyers Squibb/Otsuka, Janssen, and Neuronetics; and is/was the recipient of royalties from Lippincott Williams & Wilkins. Dr. Rado has disclosed that he is/was the recipient of grant/research support from Lilly, Otsuka, and Neuronetics and is/was a consultant/advisor to Lilly, Otsuka, and Neuronetics.

The authors have disclosed that the combinations of medications discussed in this article have not been approved by the U.S. Food and Drug Administration.

Each faculty's spouse/life partner (if any) has nothing to disclose.

All staff in a position to control the content of this CME activity and their spouses/life partners (if any) have disclosed that they have no financial relationships with, or financial interests in, any commercial companies pertaining to this educational activity.

Lippincott CME Institute, Inc., has identified and resolved all faculty and staff conflicts of interest regarding this educational activity.

Wolters Kluwer | Lippincott Williams & Wilkins  
Health | LWW.com

Lippincott Continuing Medical Education Institute, Inc. is accredited by the Accreditation Council for Continuing Medical Education to provide continuing medical education for physicians. Lippincott Continuing Medical Education Institute, Inc., designates this educational activity for a maximum of 1 *AMA PRA Category 1 Credit*<sup>™</sup>. Physicians should only claim credit commensurate with the extent of their participation in the activity. To earn CME credit, you must read the CME article(s) and complete the quiz and evaluation assessment survey on the enclosed form, answering at least 80% of the quiz questions correctly. This activity expires on January 31, 2011.

## Editor

**Philip G. Janicak, MD**

Professor of Psychiatry  
Medical Director, Psychiatric Clinical Research Center  
Rush University Medical Center, Chicago, IL

## Associate Editor

**Jeffrey T. Rado, MD**

Assistant Professor of Psychiatry  
Rush University Medical Center, Chicago, IL

## Editorial Assistant

**Sandra M. Stugis, BS**

Rush University Medical Center, Chicago, IL

## Editorial Board

**Daniel J. Carlat, MD**

Assistant Clinical Professor of  
Psychiatry, Tufts University School  
of Medicine, Boston, MA

**Mark A. Demitrack, MD**

Vice President and Chief Medical  
Officer Neuronetics, Malvern, PA

**James W. Jefferson, MD**

Clinical Professor of Psychiatry  
University of Wisconsin School of  
Medicine and Public Health  
Distinguished Senior Scientist  
Madison Institute of Medicine  
Madison, WI

**Christopher J. McDougale, MD**

Albert E. Sterne Professor and  
Chairman Department of Psychiatry  
Indiana University School of  
Medicine, Indianapolis, IN

**David N. Osser, MD**

Associate Professor of Psychiatry  
Harvard Medical School  
Taunton State Hospital  
Taunton, MA

**Rajiv Tandon, MD**

Adjunct Professor of Psychiatry  
University of Florida  
Chief of Psychiatry, Florida Office of  
Mental Health, Tallahassee, FL

Psychopharm Review (ISSN 1936-9255) is published monthly by Lippincott Williams & Wilkins, 16522 Hunters Green Parkway, Hagerstown, MD 21740-2116. Phone (800) 787-8981 or (410) 528-8572. 24-Hour Fax (410) 528-4105 or e-mail Audrey.Dyson@wolterskluwer.com. Visit our website at LWW.com. Copyright 2010 Lippincott Williams & Wilkins, Inc. All rights reserved. Priority postage paid at Hagerstown, MD, and at additional mailing offices. GST registration number: 895524239. POSTMASTER: Send address changes to Psychopharm Review Subscription Dept., Lippincott Williams & Wilkins, P.O. Box 1600, 16522 Hunters Green Parkway, Hagerstown, MD 21740-2116.

**Publisher:** Terry Materese • Customer Service Manager: Audrey Dyson

**PAID SUBSCRIBERS:** Current issue and archives (from 1999) are now available FREE online at [www.lwwnewsletters.com](http://www.lwwnewsletters.com).

Subscription rates: Personal: \$249.98 US, \$319.98 Foreign; Institutional: \$520.98 US, \$560.98 Foreign; In-Training: \$109.98 US, \$109.98 Foreign. Single copy: \$47. Send bulk pricing requests to publisher. **COPYING:** Contents of Psychopharm Review are protected by copyright. Reproduction, photocopying, and storage or transmission by magnetic or electronic means are strictly prohibited. Violation of copyright will result in legal action, including civil and/or criminal penalties. Permission to reproduce in any way must be secured in writing; e-mail [journalpermissions@lww.com](mailto:journalpermissions@lww.com). For reprints, email [matt.westcoat@wolterskluwer.com](mailto:matt.westcoat@wolterskluwer.com). Psychopharm Review is independent and not affiliated with any organization, vendor or company. Opinions expressed do not necessarily reflect the views of the Publisher, Editor, or Editorial Board. A mention of products or services does not constitute endorsement. All comments are for general guidance only; professional counsel should be sought for specific situations.

Despite the limitations to integrating an understanding of genetics and pathophysiology into clinical practice, a large number of psychotropics approved by the FDA are available for prescribers. While there are a few relatively recent and very commendable large-scale studies in adult psychiatry (Sequenced Treatment Alternatives to Relieve Depression [STAR\*D], Systematic Treatment Enhancement Program for Bipolar Disorder [STEP-BD], Clinical Antipsychotic Trials in Intervention Effectiveness [CATIE] for schizophrenia) and pediatric psychiatry (Child and Adolescent Psychiatry Trials Network [CAPTN]), evidence-based guidelines for comparative medication choices are usually lacking.<sup>2-5</sup>

In addition, polypharmacy is commonly practiced. In 1997, the American Psychiatric Practice Research Network surveyed 417 psychiatrists who were actively treating 1228 patients. At the time, 31% of their patients were receiving one psychotropic, 27.2% were receiving two, 17.5% were receiving three, and 13.6% were receiving four or more. Patients with a diagnosis of bipolar disorder received a mean of 2.8 medications; patients with schizophrenia and other psychotic disorders received a mean of 2.7 medications; and the largest group, patients with major depressive disorder and comorbid anxiety disorders, received a mean of 1.9 medications.<sup>6</sup>

When polypharmacy was specifically examined in the STEP-BD trial, three or more medications were concurrently prescribed to 40% of the participants.<sup>7</sup> Of note, complex psychopharmacology in STEP-BD was least associated with lithium, divalproex, or carbamazepine, and most often associated with second-generation antipsychotics (SGAs) and antidepressants. Patients with extensive depression histories and incomes above \$75,000 were most likely to receive polypharmacy. These trends raise concerns about the lack of adherence to evidence-based practices (i.e., mood stabilizers as the “gold standard” for bipolar disorder), the impact of advertising, and direct to consumer marketing.

**Over the last decade, pharmacotherapy in pediatric psychiatry has shown similar, if not more dramatic, trends toward polypharmacy.** Multiple epidemiologic surveys suggest that one-half to one-third of psychiatrically treated children and adolescents receive polypharmacy, with a dramatic increase in the number of youths prescribed two or more medications between 1997 and 2003.<sup>8</sup> Not surprisingly, the number of comorbid psychiatric disorders increased the risk of polypharmacy. Interestingly, coinciding with the FDA’s “black box warning” during the period of 2001–2005, the use of antidepressant *monotherapy* declined and polypharmacy increased in younger populations.

As a result, reasonable concerns are raised by third-party payers and administrators about the costs associated with multiple prescriptions of expensive newer medications. These concerns, coupled with increased adverse

effect profiles, create an opposite trend by payers and formulary gate-keepers. Their approach promotes simpler medication regimens and discourages multiple psychotropics, rationally prescribed or not. **In this review, we emphasize the need to strike a balance, considering polypharmacy in light of an emerging understanding of disease biology.**

### THE NEED FOR EARLY INTERVENTION AND PERSONALIZED TREATMENT

Psychiatric disorders manifest themselves throughout life but primarily have an age of onset in late adolescence and early adulthood. As a consequence, they have a major impact on well-being and productive lifespan. Postmortem brain research has uncovered molecular and cellular abnormalities, not dissimilar to the end-organ damage seen in other medical disorders.<sup>9-13</sup> Clinically, the higher the number of acute episodes of an illness and hospitalizations, the more refractory a patient becomes, and the worse the long-term prognosis.<sup>14</sup> Evidence from developmental neuroimaging points to the potential for normalization of neural circuits, and therefore preventive effects of early treatment in children.<sup>15,16</sup> Taken together, these data suggest a need for early intervention to prevent the full-blown development of an illness, repeated acute episodes, and the vicious cycle of illness leading to stressful environmental interactions, which in turn exacerbate the illness.<sup>17,18</sup> Such intervention could change the life trajectory of individuals at risk for a downward medico-socioeconomic spiral to a more stable, relatively healthy, integrated, and productive role in society.

There is an emerging understanding from genetic and functional genomic studies that a large number of genes (*complexity*), with a large repertoire of mutations in each gene and different combinations of mutations in different patients (*heterogeneity*), are involved in psychiatric disorders.<sup>19</sup> Moreover, most genes appear to be involved in multiple psychiatric disorders (*overlap*). Thus, modulation of their function can lead to effects in multiple symptom domains (*interdependence*).<sup>20,21</sup> In short, genes are analogous to Lego building blocks which lead in combination to normal or abnormal phenotypes. Developmental history and environment also play important roles by modulating the expression of genes (*epigenetics* and *functional genomics*). At a clinical level, this genetic landscape translates to patients:

- Being *complex* in their symptoms;
- Being *heterogeneous* inside the same *DSM* diagnostic label;
- Displaying *overlapping comorbidity* with other psychiatric, substance use, and medical disorders; and
- Needing to have their treatment *monitored and adjusted* based on these interdependencies.<sup>22</sup>

One size definitely does not fit all, so personalization of treatment is a must for good clinicians.<sup>23</sup> Moreover, the variety of genes and biological mechanisms involved in these disorders make it likely that broad-spectrum medications (such as clozapine) or combinations of medications will be more efficacious than narrowly targeted monotherapies.<sup>24</sup> **While broad-spectrum single medications provide ease of use, medication combinations permit adjustment in the dose of individual medications. In turn, this provides more flexibility and opportunities for tailoring treatment.**

By contrast, based on our emerging understanding of the genetic architecture of psychiatric disorders, the *overlap* between comorbid disorders and their possible *interdependence* affords opportunities in the opposite direction (i.e., parsimony in the number of medications used). For example, selective serotonin reuptake inhibitors (SSRIs) can target the overlap between anxiety and depression, and SGAs the overlap between mood, psychotic, and cognitive symptoms. In this context, better accounting for patients' diversity and heterogeneity within diagnostic groups needs to be implemented as part of clinical trial design; otherwise, efficacy signals may be lost in the noise and new compounds deemed failures.<sup>22</sup> **Thus, we predict that the era of blockbuster drugs is over in the light of this emerging scientific understanding.**

### HOW DO WE PRACTICE RATIONAL POLYPHARMACY GIVEN THE PAUCITY OF CLINICAL TRIAL DATA?

A large number of FDA-approved psychotropics are available for prescribers. The main classes are antipsychotics, mood stabilizers, antidepressants, and anxiolytics. Most patients are started on one medication but over time often receive multiple agents from the same or different classes.<sup>25</sup> Prescribing choices are based on a mixture of evidence-based medicine and clinical experience/"pattern recognition." Advertising by pharmaceutical companies may also play a role. At their best, combined medications provide synergistic benefits and mitigate adverse effects by using lower doses of each medication and targeting complementary physiological (compensatory) mechanisms. At their worst, they can be clinically redundant and economically wasteful, and they can worsen adverse effects.

**In psychiatry, relatively few large and rigorous studies have analyzed combining medications.** In recent years, some studies looked at SSRIs prescribed with SGAs. Overall, their results support the use of antidepressant augmentation with SGAs for major depression and obsessive-compulsive disorder.<sup>26,27</sup>

The emergence of new agents with polyreceptor activity or combination formulations may provide an alternative to the need for polypharmacy trials with existing agents. One example is agomelatine, a novel combined melatonergic

( $MT_1/MT_2$ ) agonist and serotonergic (5-HT<sub>2C</sub>) antagonist, which may act by restoring circadian rhythms and antagonizing this serotonin receptor subtype.<sup>28</sup> Interestingly, a possibly similarly acting combination of melatonin and buspirone is in clinical trials. (Data were presented at the 2009 New Clinical Drug Evaluation Unit meeting.)

In general, studies looking at combinations of medications are time-consuming, expensive, and without a perceived immediate commercial incentive for competing pharmaceutical companies who are the main sponsors of clinical trials. However, given the precedents in cardiology (notably the “polypill”), cancer, and HIV/AIDS, it is likely that more studies of combined medications will be conducted in psychiatry and provide a foundation for evidence-based prescribing practices.<sup>29</sup> In the meantime, rational heuristic approaches involving polypharmacy are needed in clinical practice and in designing clinical trials.

### A TRI-DIMENSIONAL APPROACH

Accumulating genetic, neurobiologic, pharmacologic, and clinical evidence is consistent with three broad domains:

- Anxiety disorders;
- Mood disorders; and
- Cognitive disorders (Figure 1).

Stress is a major precipitant of psychiatric disorders, acting primarily through the anxiety domain, and inducing adrenergic, cortisol-related and inflammatory molecular changes.<sup>12</sup> Based on this emerging understanding, we proposed a tri-dimensional mental landscape (3D Mindscape) model for assessing and treating psychiatric disorders (Figure 2).<sup>30</sup>

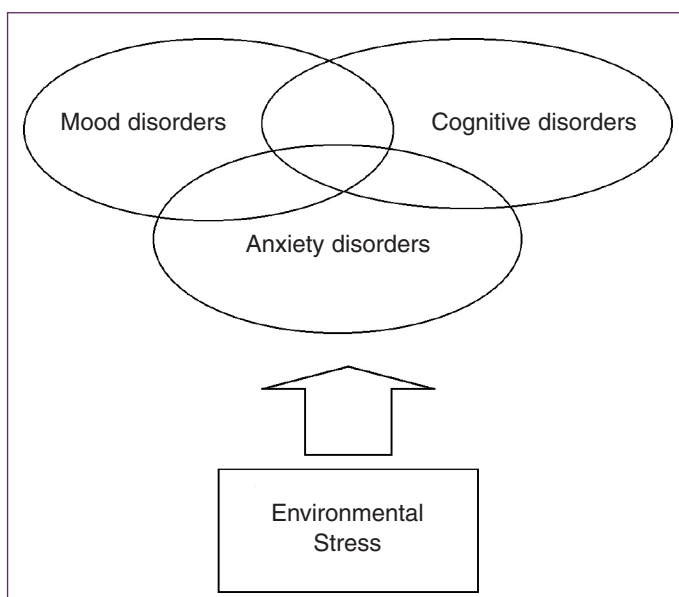


Figure 1. Overlap and interdependence of psychiatric disorders.

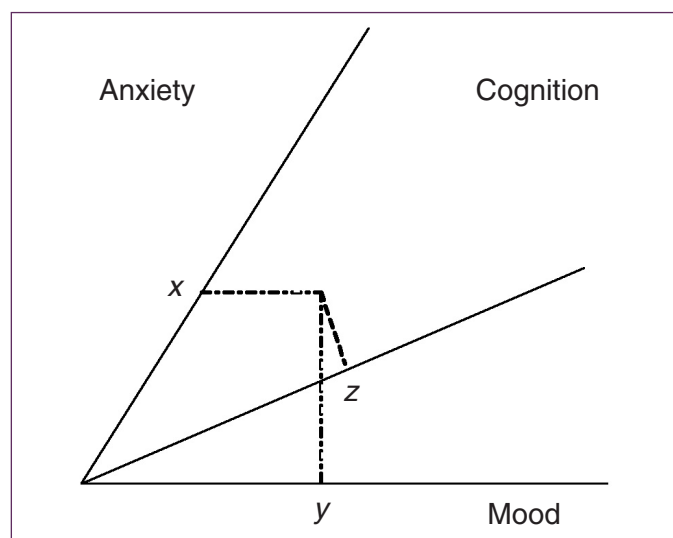


Figure 2. Mindscape tri-dimensional modeling of anxiety, mood, and cognition. At each moment in time, an individual is represented by a point with  $(x, y, z)$  coordinates in this tri-dimensional space. The sum of points over time is distributed as a cloud, unique to each individual.<sup>30</sup>

**We suggest that the psychiatry of the future may employ personalized tri-dimensional treatment (i.e., concurrent treatment of anxiety, mood, and cognitive abnormalities) plus modulation of environmental factors (e.g., stress).** Such an approach involves rational polypharmacy—the combination of three or more medications, each acting primarily on anxiety, mood, or cognition, respectively.<sup>23</sup> Depending on the major pathology, one of these medications is used at a higher dose and the others at lower doses. For example, with the major cognitive abnormalities in schizophrenia or autism, an antipsychotic may be primary at a higher dose, with an anxiolytic and/or mood stabilizer secondary at lower doses. For major mood abnormalities such as bipolar disorder, a mood stabilizer at a higher dose would be the primary approach and an anxiolytic and antipsychotic secondary at lower doses. For major anxiety abnormalities (e.g., post-traumatic stress disorder), higher-dose anxiolytic medication would be primary, with a mood stabilizer and an antipsychotic secondary at lower doses. Finally, severely ill, complex patients with major abnormalities in all three dimensions may require higher doses of all three drug classes.

**It is important to be parsimonious and rational while using polypharmacy.** One medication per dimension would be desirable although not always achievable. If more than one medication is used for optimal effects in one dimension, complementary medications, rather than redundant similar ones, should be used. Examples of possible complementary medications include:

- For the *cognitive dimension*, as in schizophrenia, lower doses of both a strong dopaminergic-blocking

antipsychotic (with primarily extrapyramidal side effects) and a broader-spectrum antipsychotic (with primarily metabolic side effects) could be used to maximize benefits and minimize adverse effects.

- For the *mood dimension*, as in bipolar disorder, lithium may be used together with an anticonvulsant mood stabilizer; and
- For the *anxiety dimension*, as in panic attacks, an SSRI may be combined with an adrenergic-blocker.

Substance abuse can also modulate one or more of the three dimensions, affecting some of the same genetic pathways as psychiatric illnesses and the medications used to treat them. For example, stimulants such as cocaine and amphetamines primarily modulate mood, hallucinogens primarily modulate cognition, and sedatives primarily modulate anxiety.<sup>20,31</sup> Alcohol can modulate all three dimensions, and at a certain dose in different individuals, can primarily impact anxiety, mood, or cognition.<sup>30,32</sup> As such, some individuals drink to be calm, others to be happy, and others to be intoxicated/dissociated from reality.<sup>32</sup> In this context, overeating can be viewed as an addiction as well.<sup>33</sup> Addictions need to be proactively probed for, uncovered, and dealt with, as addressing these underlying issues maximizes the likelihood that medications will be effective. Conversely, using medications to balance and normalize mental functioning may reduce cravings for drugs of abuse and addiction relapse. An example of this therapeutic synergy is the possible adjunctive use of an anticonvulsant, topiramate, for bipolar disorder with comorbid obesity and/or alcohol abuse.<sup>34,35</sup>

## CONCLUSIONS AND FUTURE DIRECTIONS

**There is arguably much room for improvement in the practice of psychopharmacology.** Even with available medications, we could have a more positive impact by tailoring and personalizing treatments in a rational fashion (e.g., the tri-dimensional approach described here). Ensuring that patients are adherent with treatments is a critical step. These avenues are interrelated in that better-tailored treatments lead to more stable and insightful patients and to fewer adverse effects, both of which increase medication adherence. Using pill-reminder devices and medications with longer half-lives (including depot medications) can also improve adherence and outcomes. Avoiding overmedication (e.g., not maintaining long-term outpatients on the medication doses needed for acute inpatient stabilization) and consequent hedonic blunting can preserve quality of life and reduce urges to compensate with drugs of abuse.

**In addition to the right treatment, the right dose and the right duration are important.** A successful treatment should start early at sufficient doses with the “right fit” of medications to stop the illness before it

evolves. While this approach is obvious in its merits for diseases such as cancer, it should also be pursued for psychiatric illnesses.

### *Diagnostic Precision*

Genetic and biomarker testing now on the horizon will facilitate objective assessment of disease risk (e.g., genetic testing), disease severity, and monitoring of response to treatment (e.g., biomarker tests).<sup>19,36</sup> While genetic testing for mutations in deoxyribonucleic acid (DNA) gives the earliest detection of a potential problem even before illness occurs, it is not very precise (i.e., many genes and environmental factors contribute over time to the manifestation of a phenotype that may or may not occur). Thus, most single genetic mutations have a weak connection to the ultimate clinical presentation. Because of the heterogeneity of the human population and the complexity of most psychiatric disorders, genetic-only testing will not likely be powerful and informative enough by itself. On the other end, neuropsychological testing can be precise, but this is more the case when the disease has already manifested itself and can be readily diagnosed using clinical criteria. Moreover, a complicating factor is that people who are ill with a psychiatric disorder (e.g., schizophrenia) may not always be able or willing to report their symptoms accurately.

Blood or cerebrospinal fluid biomarkers, such as ribonucleic acid (RNA) or protein levels, are a reasonable compromise between early detection and later precision. The interaction of genes with the environment leads to gene expression (RNA production), which is, in essence, a biological endophenotype (internal building block for phenotype). In turn, this underlies the production of proteins and the subsequent manifestation of an external phenotype (such as symptomatic clinical illness). As such, with biomarkers only, one could detect problems earlier (allowing for early intervention or prevention efforts) and fairly precisely in terms of relationship to phenotype. Single time-point testing of an individual could provide information related to state and clinical severity.<sup>36</sup> Repeated measures over time could provide information related to treatment response and trait-personalized diagnosis. Comprehensive approaches, integrating genetic testing, biomarkers, and neuropsychological (phenotypic) testing will increase the yield in terms of combining earlier detection with better precision, as well as trait with state. Such testing will likely become indispensable in choosing medications and making other clinical decisions.

### *Medication Tolerance or Resistance*

**After choice of medications and nonadherence, medication tolerance or resistance may be the third most important and underappreciated cause of psychiatric treatment failure.** As a result, it represents a

massive burden to patients, health care providers, drug developers, and society. As in cancer, infectious diseases, or cardiovascular disorders, most long-term medication therapies in psychiatry need to involve multiple agents, as patients on single drugs (or single-target drugs) can develop tolerance and resistance.

To prevent, delay, or reverse resistance, the whole patient and lifestyle must be taken into account. For optimal outcomes, it is also important to address medical comorbidities. The limited genetic repertoire of humans means that there are shared genes and molecular mechanisms between different diseases, including psychiatric and nonpsychiatric disorders.<sup>36-38</sup> As a positive practical consequence, there are “two-for-one” opportunities for therapeutic synergizing and minimizing the total number of agents a patient needs. For example, medications for cardiovascular disorders (e.g., adrenergic-blockers) may also be used to treat anxiety disorders.<sup>39</sup> Medications for cancer (e.g., protein kinase C inhibitors) might also be used to treat mood disorders.<sup>40</sup> Medications for endocrine disorders (e.g., gonadal steroid hormones and their precursors) may be of use in schizophrenia.<sup>41-43</sup>

### Addressing Environmental Factors

**It is equally important to modulate environmental factors that can have major effects on gene expression and responsiveness to pharmacologic treatment.** Thus, we are not victims of our genes, and in many cases, our genes are victims of us! Environmental toxins (including substance abuse, negative interpersonal relationships, social isolation) may be as detrimental as internal (genetically inherited) abnormalities.<sup>21</sup> Conversely, a positive and favorable environment can mitigate internal abnormalities, such as genetic predisposition to illness. Stress can be modulated through a variety of approaches, including cognitive-behavioral, exercise, sleep, hygiene, diet, and other environmental choices.<sup>44,45</sup> *Omega-3 fatty acids* are emerging as a particularly interesting and relatively safe dietary supplementation strategy, as is possible supplementation with *vitamin D* when sun exposure is limited or contraindicated.<sup>46,47</sup> Regular moderate *physical exercise* may be as beneficial for psychiatric disorders as for other medical disorders by promoting homeostatic balance and system robustness, as well as enhancing neurogenesis and growth factors. As such, this validates the ancient Roman wisdom of *mens sana in corpore sano* (a healthy mind in a healthy body).<sup>48-50</sup> By extrapolation, a treadmill may be a better implement in a therapist's office than a couch.

### REFERENCES

1. Regier DA. Dimensional approaches to psychiatric classification: refining the research agenda for DSM-V: an introduction. *Int J Methods Psychiatr Res* 2007;16(suppl 1):S1-S5.
2. Rush AJ, Warden D, Wisniewski SR, et al. STAR\*D: revising conventional wisdom. *CNS Drugs* 2009;23(8):627-647.
3. Schneck CD, Miklowitz DJ, Miyahara S, et al. The prospective course of rapid-cycling bipolar disorder: findings from the STEP-BD. *Am J Psychiatry* 2008;165(3):370-377.
4. Swartz MS, Wagner HR, Swanson JW, et al. The effectiveness of antipsychotic medications in patients who use or avoid illicit substances: results from the CATIE study. *Schizophr Res* 2008;100(1-3):39-52.
5. Shapiro M, Silva SG, Compton S, et al. The child and adolescent psychiatry trials network (CAPTN): infrastructure development and lessons learned. *Child Adolesc Psychiatry Ment Health* 2009;3(1):12.
6. Pincus HA, Zarin DA, Tanielian TL, et al. Psychiatric patients and treatments in 1997: Findings from the American Psychiatric Practice Research Network. *Arch Gen Psychiatry* 1999;56(5):441-449.
7. Goldberg JF, Brooks JO 3rd, Kurita K, et al. Depressive illness burden associated with complex polypharmacy in patients with bipolar disorder: findings from the STEP-BD. *J Clin Psychiatry* 2009;70(2):155-162.
8. McIntyre RS, Jerrell JM. Polypharmacy in children and adolescents treated for major depressive disorder: a claims database study. *J Clin Psychiatry* 2009;70(2):240-246.
9. Benes FM. Amygdalocortical circuitry in schizophrenia: from circuits to molecules. *Neuropsychopharmacology* September 2, 2009. Epub ahead of print.
10. Katsel P, Davis KL, Haroutunian V. Variations in myelin and oligodendrocyte-related gene expression across multiple brain regions in schizophrenia: a gene ontology study. *Schizophr Res* 2005;79(2-3):157-173.
11. McNamara RK, Jandacek R, Rider T, et al. Deficits in docosahexaenoic acid and associated elevations in the metabolism of arachidonic acid and saturated fatty acids in the postmortem orbitofrontal cortex of patients with bipolar disorder. *Psychiatry Res* 2008;160(3):285-299.
12. Karssen AM, Her S, Li JZ, et al. Stress-induced changes in primate prefrontal profiles of gene expression. *Mol Psychiatry* 2007;12(12):1089-1102.
13. Evans SJ, Choudary PV, Neal CR, et al. Dysregulation of the fibroblast growth factor system in major depression. *Proc Natl Acad Sci U S A* 2004;101(43):15506-15511.
14. Frye MA, Ketter TA, Leverich GS, et al. The increasing use of polypharmacotherapy for refractory mood disorders: 22 years of study. *J Clin Psychiatry* 2000;61(1):9-15.
15. Shaw P, Lalonde F, Lepage C, et al. Development of cortical asymmetry in typically developing children and its disruption in attention-deficit/hyperactivity disorder. *Arch Gen Psychiatry* 2009;66(8):888-896.
16. Shaw P, Sharp WS, Morrison M, et al. Psychostimulant treatment and the developing cortex in attention deficit hyperactivity disorder. *Am J Psychiatry* 2009;166(1):58-63.

17. Salvatore G, Drevets WC, Henter ID, et al. Early intervention in bipolar disorder, Part I: Clinical and imaging findings. *Early Interv Psychiatry* 2008;2(3):122–135.
18. Salvatore G, Drevets WC, Henter ID, et al. Early intervention in bipolar disorder, Part II: Therapeutics. *Early Interv Psychiatry* 2008;2(3):136–146.
19. Le-Niculescu H, Patel SD, Bhat M, et al. Convergent functional genomics of genome-wide association data for bipolar disorder: Comprehensive identification of candidate genes, pathways, and mechanisms. *Am J Med Genet B Neuropsychiatr Genet* 2009;150B(2):155–181.
20. Le-Niculescu H, Balaraman Y, Patel S, et al. Towards understanding the schizophrenia code: an expanded convergent functional genomics approach. *Am J Med Genet B Neuropsychiatr Genet* 2007;144B(2):129–158.
21. Le-Niculescu H, McFarland MJ, Ogden CA, et al. Phenomic, convergent functional genomic, and biomarker studies in a stress-reactive genetic animal model of bipolar disorder and comorbid alcoholism. *Am J Med Genet B Neuropsychiatr Genet* 2008;147B(2):134–166.
22. Niculescu AB, Lulow LL, Ogden CA, et al. Phenochipping of psychotic disorders: a novel approach for deconstructing and quantitating psychiatric phenotypes. *Am J Med Genet B Neuropsychiatr Genet* 2006;141B(6):653–662.
23. Niculescu AB 3rd. Polypharmacy in oligopopulations: What psychiatric genetics can teach biological psychiatry. *Psychiatr Genet* 2006;16(6):241–244.
24. Kim DH, Maneen MJ, Stahl SM. Building a better antipsychotic: Receptor targets for the treatment of multiple symptom dimensions of schizophrenia. *Neurotherapeutics* 2009;6(1):78–85.
25. Kingsbury SJ, Yi D, Simpson GM. Psychopharmacology: Rational and irrational polypharmacy. *Psychiatr Serv* 2001;52(8):1033–1036.
26. Papakostas GI, Shelton RC, Smith J, et al. Augmentation of antidepressants with atypical antipsychotic medications for treatment-resistant major depressive disorder: a meta-analysis. *J Clin Psychiatry* 2007;68(6):826–831.
27. Vulink NC, Denys D, Fluitman SB, et al. Quetiapine augments the effect of citalopram in non-refractory obsessive-compulsive disorder: a randomized, double-blind, placebo-controlled study of 76 patients. *J Clin Psychiatry* 2009;70(7):1001–1008.
28. Goodwin GM, Emsley R, Rembry S, et al. Agomelatine prevents relapse in patients with major depressive disorder without evidence of a discontinuation syndrome: a 24-week randomized, double-blind, placebo-controlled trial. *J Clin Psychiatry* 2009;70(8):1128–1137.
29. Yusuf S, Pais P, Afzal R, et al. Effects of a polypill (Polycap) on risk factors in middle-aged individuals without cardiovascular disease (TIPS): a phase II, double-blind, randomised trial. *Lancet* 2009;373(9672):1341–1351.
30. Niculescu AB 3rd, Schork NJ, Salomon DR. Mindscape: a convergent perspective on life, mind, consciousness, and happiness. *J Affect Disord* 2009. Epub ahead of print.
31. Ogden CA, Rich ME, Schork NJ, et al. Candidate genes, pathways, and mechanisms for bipolar (manic-depressive) and related disorders: an expanded convergent functional genomics approach. *Mol Psychiatry* 2004;9(11):1007–1029.
32. Rodd ZA, Bertsch BA, Strother WN, et al. Candidate genes, pathways and mechanisms for alcoholism: an expanded convergent functional genomics approach. *Pharmacogenomics J* 2007;7(4):222–256.
33. Lutter M, Nestler EJ. Homeostatic and hedonic signals interact in the regulation of food intake. *J Nutr* 2009;139(3):629–632.
34. Roy Chengappa KN, Schwarzman LK, Hulihan JF, et al. Adjunctive topiramate therapy in patients receiving a mood stabilizer for bipolar I disorder: a randomized, placebo-controlled trial. *J Clin Psychiatry* 2006;67(11):1698–1706.
35. Kenna GA, Lomastro TL, Schiesl A, et al. Review of topiramate: an antiepileptic for the treatment of alcohol dependence. *Curr Drug Abuse Rev* 2009;2(2):135–142.
36. Le-Niculescu H, Kurian SM, Yehyaw N, et al. Identifying blood biomarkers for mood disorders using convergent functional genomics. *Mol Psychiatry* 2009;14(2):156–174.
37. Clamp M, Fry B, Kamal M, et al. Distinguishing protein-coding and non-coding genes in the human genome. *Proc Natl Acad Sci U S A* 2007;104(49):19428–19433.
38. Torkamani A, Topol EJ, Schork NJ. Pathway analysis of seven common diseases assessed by genome-wide association. *Genomics* 2008;92(5):265–272.
39. Taylor FB, Martin P, Thompson C, et al. Prazosin effects on objective sleep measures and clinical symptoms in civilian trauma post-traumatic stress disorder: a placebo-controlled study. *Biol Psychiatry* 2008;63(6):629–632.
40. Zarate CA, Manji HK. Protein kinase C inhibitors: Rationale for use and potential in the treatment of bipolar disorder. *CNS Drugs* 2009;23(7):569–582.
41. Maninger N, Wolkowitz OM, Reus VI, et al. Neurobiological and neuropsychiatric effects of dehydroepiandrosterone (DHEA) and DHEA sulfate (DHEAS). *Front Neuroendocrinol* 2009;30(1):65–91.
42. Bergemann N, Parzer P, Kaiser D, et al. Testosterone and gonadotropins but not estrogen associated with spatial ability in women suffering from schizophrenia: a double-blind, placebo-controlled study. *Psychoneuroendocrinology* 2008;33(4):507–516.
43. Ko YH, Lew YM, Jung SW, et al. Short-term testosterone augmentation in male schizophrenics: a randomized, double-blind, placebo-controlled trial. *J Clin Psychopharmacol* 2008;28(4):375–383.
44. Collins A, Hill LE, Chandramohan Y, et al. Exercise improves cognitive responses to psychological stress through

enhancement of epigenetic mechanisms and gene expression in the dentate gyrus. *PLoS One* 2009;4(1):e4330.

45. Lucas M, Dewailly E, Blanchet C, et al. Plasma omega-3 and psychological distress among Nunavik Inuit (Canada). *Psychiatry Res* 2009;167(3):266–278.
46. McNamara RK. Evaluation of docosahexaenoic acid deficiency as a preventable risk factor for recurrent affective disorders: current status, future directions, and dietary recommendations. *Prostaglandins Leukot Essent Fatty Acids* 2009;81(2–3):223–231.
47. Hoogendijk WJ, Lips P, Dik MG, et al. Depression is associated with decreased 25-hydroxyvitamin D and increased

parathyroid hormone levels in older adults. *Arch Gen Psychiatry* 2008;65(5):508–512.

48. Niculescu AB. Genomic studies of mood disorders: the brain as a muscle? *Genome Biol* 2005;6(4):215.
49. Strohle A, Stoy M, Graetz B, et al. Acute exercise ameliorates reduced brain-derived neurotrophic factor in patients with panic disorder. *Psychoneuroendocrinology* August 12, 2009. Epub ahead of print.
50. van Praag H, Shubert T, Zhao C, et al. Exercise enhances learning and hippocampal neurogenesis in aged mice. *J Neurosci* 2005;25(38):8680–8685.

## Psychopharm Review

# CME QUIZ

**Online quiz instructions:** To take the quiz online, go to <http://cme.LWWnewsletters.com>, and enter your *username* and *password*. Your *username* will be the letters **LWW** (case sensitive) followed by the 12-digit account number on your mailing label. You may also find your account number on the paper answer form mailed with your issue. Your *password* will be **1234**; this password may not be changed. Follow the instructions on the site. You may print your official certificate *immediately*. Please note: Lippincott CME Institute, Inc., will not mail certificates to online participants.

**Online quizzes expire at 11:59 pm Pacific Standard Time on the due date.**

**Select the best answer and use a blue or black pen to completely fill in the corresponding box on the enclosed answer form.** Please indicate any name and address changes directly on the answer form. If your name and address do not appear on the answer form, please print that information in the blank space at the top left of the page. Make a photocopy of the completed answer form for your own files and send the original answer form to Lippincott Williams & Wilkins, Office of Continuing Education Department, P.O. Box 1543, Hagerstown, MD 21741-9914 by **January 31, 2011**. For more information, call (800) 787-8981. The CME credits are included in the subscription price.

1. Studies useful for comparative evidence-based prescribing are
  - A. STAR\*D
  - B. STEP-BD
  - C. CATIE
  - D. All of the above
2. Psychiatric genetics is implicating many different genes for each psychiatric disorder.
  - A. True
  - B. False
3. Studies analyzing combined medications are relatively rare in which of the following fields of medicine?
  - A. Infections disease
  - B. Oncology
  - C. Psychiatry
  - D. All of the above
4. A rational psychopharmacologic approach could involve the combination of three or more medications, each acting primarily on anxiety, mood, or cognition. Depending on where the major pathology is, one of the medications is used at a higher dose and the others at lower doses.
  - A. True
  - B. False
5. There is room for improvement in the practice of psychopharmacology with available medications.
  - A. True
  - B. False