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## 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

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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.

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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>

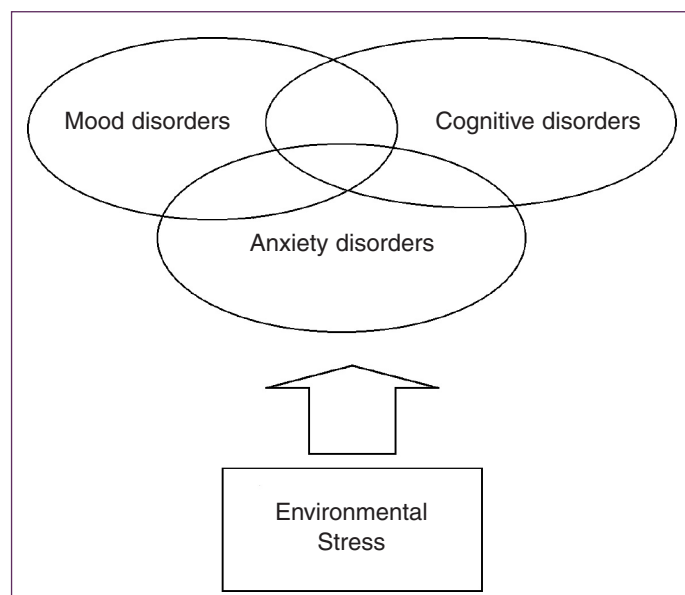


Figure 1. Overlap and interdependence of psychiatric disorders.

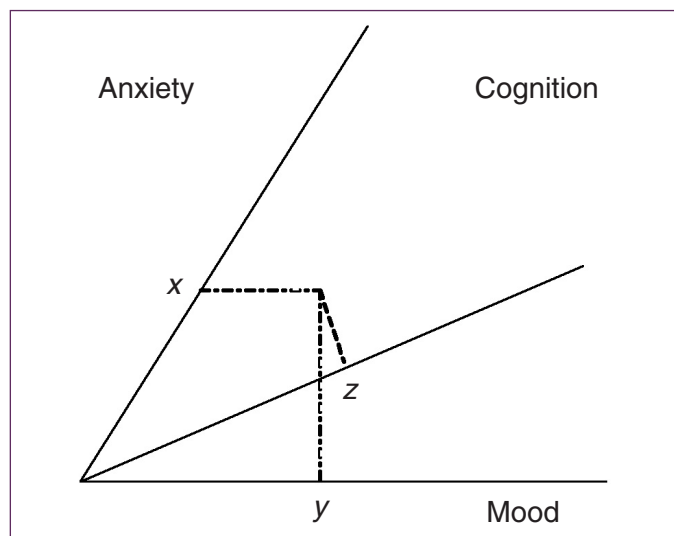


Figure 2. Mindscape tri-dimensional modeling of anxiety, mood, and cognition. At each moment in time, an individual is represented by a point with  $(x, y, z)$  coordinates in this tri-dimensional space. The sum of points over time is distributed as a cloud, unique to each individual.<sup>30</sup>

**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.

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## Psychopharm Review

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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