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The Impact of Neurochemical Mediators on Antidepressant Effectiveness

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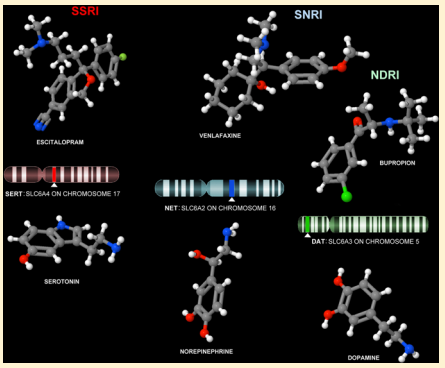
ABSTRACT: Despite marked differences in the psychobiological profiles of depressed patients, clinical research has not supported selection of antidepressant (AD) medications based on neurochemistry. Prescribers have been advised to start all patients on the same class of ADs and then switch or combine them until benefit is achieved. New research may transform this practice. By matching clinical moderators to neurochemical mediators, health professionals may finally be able to overcome the disappointing remission rates associated with initial AD treatments and avoid the progressively worsening results associated with current trial and error approaches.



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For the past 60 years, neuroscientists have gathered abundant evidence that the indoleamine serotonin and the catecholamines norepinephrine and dopamine (Figure 1) serve diverse functions in the CNS. All widely used ADs affect monoaminergic neurotransmission, and these mechanisms of action are likely to be utilized by most, if not all, medications in this category for years to come. Yet clinicians, who frequently select ADs based on patient characteristics, have long been taught that neurotransmitter mechanisms do not matter because, as stated by the American Psychiatric Association: "the effectiveness of ADs is generally comparable between classes and within classes of medications..."[1] This conclusion derives primarily from pharmaceutical industry-funded clinical trials that have recruited undifferentiated depressed populations and are neither designed nor powered to uncover differences in AD effectiveness for particular types of patients. These undetected differences are not trivial. They lead to increased morbidity and mortality for patients who do not remit, and have been an inadequately acknowledged consequence of the methodological limitations of randomized clinical trials.

Studies examining moderators and mediators of successful depression treatment have suggested new possibilities. Moderators identify for whom and under what conditions therapeutic effects occur. Mediators identify how and why they occur. Investigations of this type are confirming the long recognized heterogeneity of depressed patients and their need for different types of treatments. Genetic polymorphisms that moderate susceptibility to various ADs may be useful in identifying subtypes of patients more likely to benefit from different monoaminergic mediators. Best known among these are the L and S variants of the 5-HTTLPR (5-hydroxytryptamine transporter length polymorphic region) of the serotonin transporter (SERT) gene, each of which has been associated with increased SSRI responsiveness in certain populations. Also of interest are several 5-HT receptor gene variations, which have been shown to mediate SSRI effectiveness and side-effect susceptibility. Outside of the SSRIs, The T-allele of the NET (norepinephrine transporter) T-182C polymorphism has been associated with greater therapeutic response to an SNRI. The minor "A" allele of rs27072, which down-regulates dopamine transporter (DAT) expression, has been linked to bipolar disorder and stimulant-like protective effects in ADHD. Additionally, the *Taq*IA polymorphism of the *DRD2* gene has been correlated with blunted responses to pleasurable eating and increased bupropion effectiveness in smoking cessation. Whether genetic differences like these will have clinically useful roles as biomarkers for particular AD treatments remains to be seen. The multifactorial nature of AD response will continue to challenge all research in this area.

While these processes are being investigated, renewed interest and funding are being directed toward matching depressed patients with effective ADs as early as possible in the course of the disorder. These efforts are fueled by persuasive evidence that failure to achieve remission from first-step treatments leads to a progressive decrease in the likelihood of achieving remission after subsequent steps. In the STAR*D study, the largest naturalistic AD investigation ever conducted, the number of patients remitting after the first and last of four sequential treatment steps decreased from 1085 to 15, while dropout rates increased progressively from 27% to 60%. (Figure 2) When later

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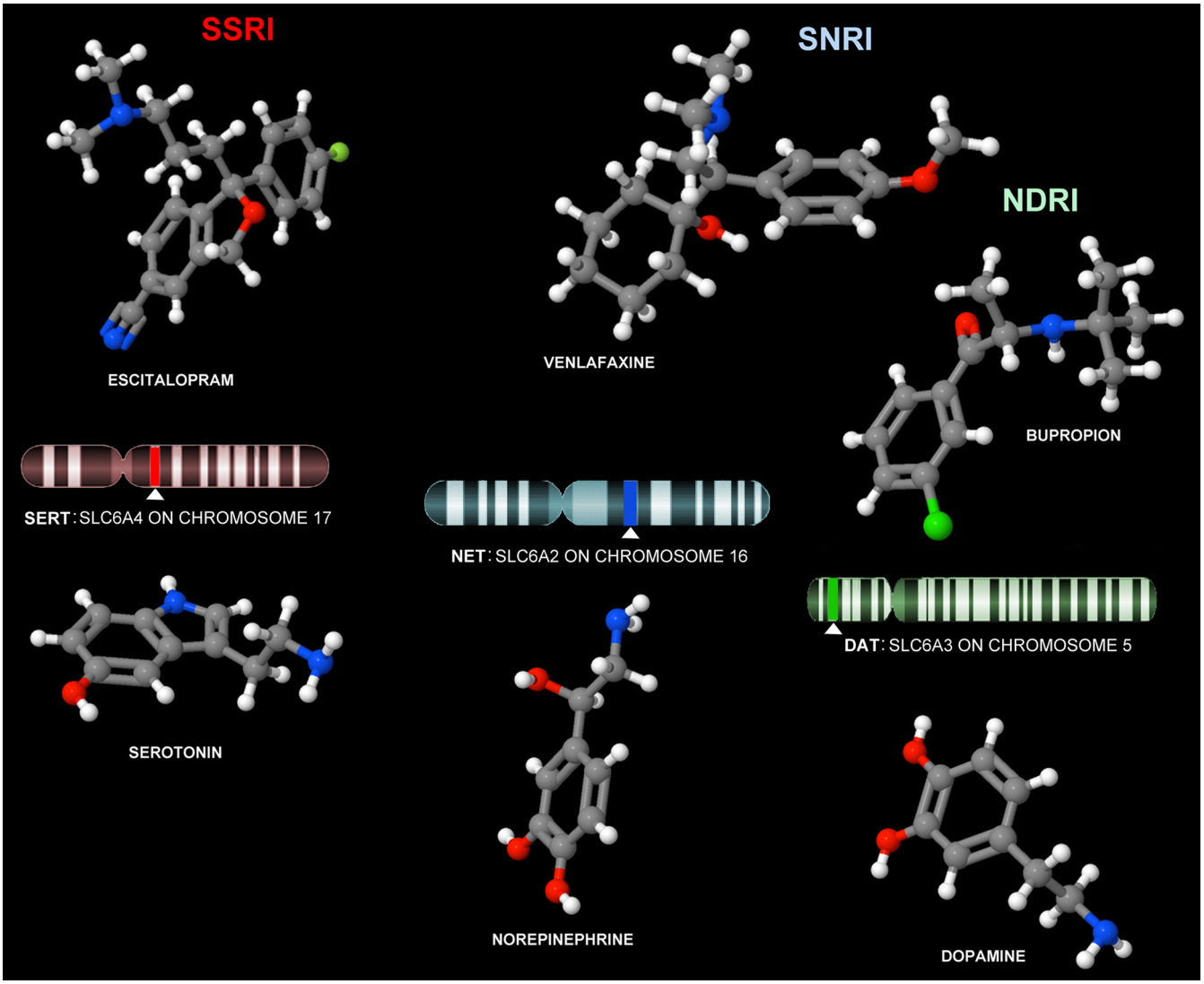

Figure 1. Classes of selective ADs, potential moderator sites on transporter-encoding chromosomes, and monoamine neurotransmitters. The key to personalizing AD treatments will be the discovery of clinically useful genetic and epigenetic biomarkers for individual differences in synthesis, release, receptor activity, reuptake, and downstream effects of mediating neurochemicals.

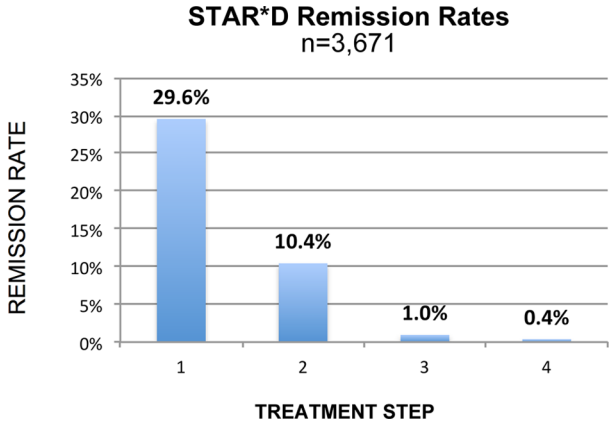

Figure 2. Remission rates shown here reflect the number of remitted patients at each step relative to the total.[2] Adding up these percentages indicates a cumulative remission rate of only 41.4%.

remissions occurred, the probability of relapse and residual dysfunction increased with each step. Treatments were based on predetermined sequences unmatched to clinical characteristics, for example, Step 1: SSRI, Step 2: NDRI or SNRI, and so forth. Unlike the remission rates shown in Figure 2, the larger numbers reported in the study were calculated with reference to the diminishing number of patients entering each treatment step.[2]

Clinical medicine offers many examples of imperfect interventions allowing pathological conditions to progress; however, the decreasing benefits from ADs signal the need for improved therapeutic guidelines. The quest for biomarkers has inspired renewed attention to the mechanisms controlling the expression and operation of monoamine neurotransmitter systems. Given how much is already known about them, for example, dopamine's role in motivation and serotonin's effect on emotional regulation, one might readily question the rationale for ignoring neurotransmitter differences in treating individual cases. The justification given has been that all monoamine effects on depression are likely to be mediated by shared downstream mechanisms. The evidence, however, does not support dismissing neurotransmitter differences. The well-replicated finding that experimental depletion of CNS serotonin immediately reproduces depressive symptoms in patients who have

remitted on serotonergic, but not catecholaminergic ADs, and vice versa, suggests that discrete mechanisms mediate the therapeutic effects of these medications. The high number of dropouts reported in the STAR*D study points to the probability that when ADs are prescribed without targeting treatments to individual needs, patients may simply "get off the elevator" rather than keep going in the wrong direction.

Let us consider two hypothetical cases depicting the possibility of a more individualized approach to AD selection. Mrs. J is a 72-year-old woman who presents for the first time after years of sadness, anxiety, anger, irritability, insomnia, and nonspecific body pains. Her family practitioner initiates the SNRI duloxetine, because it is promoted to doctors for pain relief. At her return appointment 2 weeks later, she says that she feels much worse and speaks of "wanting to die." Her physician refers her to a university-based psychiatrist, who orders specialized peripheral blood cell assays. Chronoamperometry indicates diminished serotonin uptake rates, while quantitative ligand binding assays evidence reduced surface SERT binding.[3] These results suggest diminished CNS serotonin activity and lead to genotyping, which reveals a *Tph2* single nucleotide polymorphism (SNP) associated with low TPH activity and correspondingly reduced serotonin synthesis. Based on this evaluation, the patient is switched from duloxetine to the SSRI escitalopram plus 5-hydroxytryptophan. The 5-HTP supplies the substrate that the *Tph2* SNP restricts, restoring intraneuronal serotonin synthesis and preventing SSRI-induced SERT blockade from reducing rather than increasing serotonergic neurotransmission. Within weeks she is improved and without suicidal ideation, but she continues to experience intermittent feelings of agitation, which she says started after taking duloxetine.

Contrast her case with that of Mr. W, a 55-year-old accountant, who is referred to a psychiatrist because of depression with apathy and fatigue. The psychiatrist administers several tests including a computerized decision support system (CDSS) that matches moderators to mediators using a measurement-based algorithm. The psychiatrist concludes that Mr. W needs an NDRI and starts the patient on bupropion. One month later, Mr. W is in remission according to both mental status examination and standardized testing (HDRS-17) and describes himself as feeling "normal" again.

Mrs. J's doctor decided to treat her initially with duloxetine, because evidence-based medicine and the FDA have sanctioned duloxetine for relief of fibromyalgia and other chronic pain conditions. Unfortunately, there are no similarly sanctioned guidelines for matching patients with diverse depressive profiles to ADs with different mechanisms of action. Many studies have indicated, however, that serotonergic agents can be effective in reducing anxiety, anger, and irritability, while catecholaminergic medications can increase energy and motivation. Although Mrs. J's depression improved after receiving personalized treatment, her condition did not return to baseline. Would she have been better off if a measurement-based algorithm assessing symptoms and biomarkers had guided her initial treatment? In a naturalistic multisite sample that we have studied, the remission rate for first-step AD treatment with measurement-based guidance was 65% compared with a significantly lower rate of 42% for measurement-based guidance following unsuccessful standard treatment.[4]

Are these later-step patients simply more difficult to treat, or have they been adversely affected by their initial treatment? Perhaps there is a useful parallel in the way that childhood trauma can negatively affect adult brain function. As Archer et al. stated: "...it is increasingly evident that epigenetic mechanisms mediate the gene-environment dialog in early life, thereby providing persistent epigenetic programming of adult neurophysiology dysfunctions and dysregulations."[5] Phenoconversion is another mechanism to consider. In a recent study of *CYP2D6* metabolizer status, the incidence of poor metabolizer status based on phenotype was almost seven times higher than that expected on the basis of geneotype. According to the authors, their results demonstrated that "personalized medicine based solely on genetics can be misleading" and supported "the need to consider drug-induced variability as well."[6] Little is known about epigenetic changes that might result from AD treatment or the role of phenoconversion in diminishing the effectiveness of repeated AD treatment steps, but these and other processes that might interfere with therapeutic benefits merit further investigation (Figure 3).

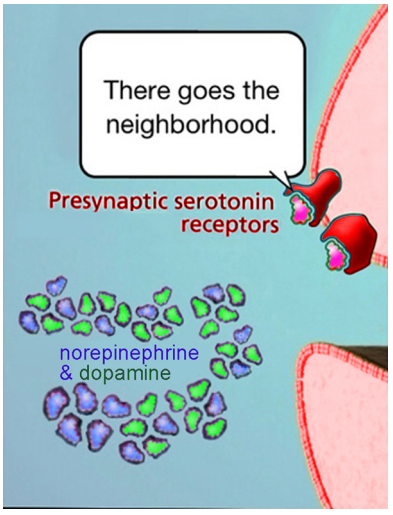

Figure 3. Receiving the wrong first-step AD may initiate maladaptive changes that compromise the effectiveness of later treatments. (Figure adapted with permission from ref 7 and Canadian Medical Association.)

As more is learned about AD moderators, preclinical understanding of monoamine mediators will be increasingly significant, whether elaborating mechanisms that enhance or detract from treatment effectiveness. Given the worldwide cost of depressive disorders in both human and economic terms, clinical researchers, practitioners, and policy-makers need to pay careful attention to what neuroscience has to teach about current and future treatments.

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Notes

The authors declare the following competing financial interest(s): R. Metzner received lecture fees for speaking about the individualized treatment of depression prior to 2010 from Pfizer, Wyeth, GlaxoSmithKline, Forest Laboratories, Bristol-Myers Squibb, Otsuka, Medical World Conferences/Antidote, and Postgraduate Institute of Medicine. Based on a method he patented (U.S. patent 7,553,834), a symptom-moderated computerized decision support system has been accessible

without charge for use by health professionals and researchers online since 2005 and has been sold as a mobile app since 2012.

■ ABBREVIATIONS

5-HIAA, 5-hydroxyindoleacetic acid; 5-HT, serotonin; 5-HTP, 5-hydroxytryptophan; 5-HTTLPR, serotonin transporter length polymorphic region; AD, antidepressant; ADHD, attention deficit hyperactivity disorder; CDSS, computerized decision support system; CNS, central nervous system; CYP2D6, cytochrome P450 2D6; DA, dopamine; DAT, dopamine transporter; DRD2, dopamine receptor D2; FDA, Food and Drug Administration; HDRS-17, Hamilton Depression Rating Scale −17 items; HPLC, high performance liquid chromatography; L, long; L-DOPA, L-dyhdroxyphenylalanine; MAO, monoamine oxidase; NDRI, norepinephrine dopamine reuptake inhibitor; NET, norepinephrine transporter; PBC, peripheral blood cell; PCR, polymerase chain reaction; SERT, serotonin transporter; S, short; SNP, single nucleotide polymorphism; SNRI, serotonin norepinephrine reuptake inhibitor; SSRI, selective serotonin reuptake inhibitor; STAR*D, Sequenced Treatment Alternatives to Relieve Depression; TPH, tryptophan hydroxylase

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