A saga of psychiatric serendipities…

…and of evolutions, paradigm shifts, and radical breakthroughs in psychiatric therapies.

For a relatively young medical discipline like psychiatry, the history of discovery of biological therapeutics is replete with twists and turns, the pace of which will likely not abate. These discoveries can be initiated by both observant clinicians and dedicated researchers.

As I contemplated the scientific saga of developing somatic and pharmaceutical treatments for major psychiatric disorders, I recognized several interesting themes: *serendipity*, *evolution*, *paradigm shifts*, and *radical breakthroughs*. Consider the following examples of those themes.

Neuromodulation

Electroconvulsive therapy (ECT), the original neuromodulation therapy, was discovered (*serendipity*) when Meduna, mistakenly thinking that schizophrenia and epilepsy are "antagonistic," used camphor and, later, metrazol, to induce seizures to treat schizophrenia. Later, Cerletti and Bini switched the seizure induction to electricity (*evolution*), and the use of ECT spread, like a seizure, around the world after their initial report. Later, unilateral ECT and pulse wave ECT were developed to reduce the incidence of side effects (further evolution).

In contemporary psychiatry, a *paradigm shift* in neuromodulation techniques has emerged over the past decade with the development of an array of novel neuromodulation techniques,[1] some of which do not induce seizures or touch the scalp with electrodes—or even use electricity. These techniques include vagus nerve stimulation, repetitive transcranial magnetic stimulation, epidural cortical stimulation, focused ultrasound, low-field magnetic stimulation, transcranial direct current stimulation, and magnetic seizure therapy. Currently (pun intended!), radical breakthroughs with significant therapeutic promise are being developed, such as optogenetic stimulation and deep brain stimulation.

Antipsychotics

One of the most momentous *serendipitous* discoveries in psychiatry (one that should have won the Nobel Prize in Medicine or Physiology, like the discovery of penicillin) was the phenothiazine drug chlorpromazine, first used as an adjunct to surgical anesthesia in the late 1940s and early 1950s.[2] Chlorpromazine eliminated psychotic symptoms in many patients (refuting centuries of dogma that madness is irreversible), led to deinstitutionalization and community care of patients who suffer a serious psychiatric disorder, and reduced psychiatric beds from 50% of all hospital beds in the United States to about 5% today. Numerous phenothiazines were developed (*evolution*) followed by six non-phenothiazine classes (*paradigm shift*).

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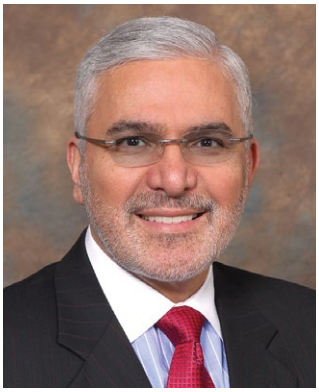

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Never underestimate the importance of serendipity in generating new insights that lead to transformative paradigm shifts in treatment

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Another truly felicitous *serendipity* was the discovery of the first atypical antipsychotic, clozapine (synthesized in 1959, the same year that the antipsychotic thioridazine [Mellaril] was synthesized), which was initially shelved because it did *not* cause extrapyramidal symptoms (EPS); at the time, EPS were erroneously thought to be indispensable for antipsychotic efficacy! The discovery of clozapine led to the development of the nine atypical antipsychotics that have largely replaced the first-generation agents (*paradigm shift*) and that mimic clozapine's far stronger binding of serotonin 5-HT2A receptors than binding of dopamine D2 receptors, thus reducing the occurrence of neurologic movement disorders (ie, EPS).

Clozapine led to a *radical breakthrough* when it proved to have efficacy in schizophrenia that is refractory to first-generation antipsychotics (the CATIE study showed the same efficacy for second-generation antipsychotics). A follow-up *breakthrough* was the discovery of the efficacy of clozapine on suicidality, a significant cause of mortality in patients with schizophrenia.

A recently reported treatment for schizophrenia might be a potentially *radical breakthrough*. In a pilot study, researchers reported very rapid and significant improvement in positive and negative symptoms (and even anxiety and depressive symptoms, and within 4 hours and persisting for 4 weeks![3]), using the antihypertensive sodium nitroprusside, administered IV. Here is another paradigm shift—in drug delivery, similar to what was seen with IV ketamine, which led to a *radical breakthrough* in treating drug-resistant depression.

Interestingly, the *N*-methyl-D-aspartate (NMDA) receptor is playing a key role in radical breakthroughs in schizophrenia and depression. A glycine transporter I inhibitor (which potentiates what is strongly suspected to be a hypofunctional NMDA receptor in schizophrenia) is undergoing further study for the treatment of negative and residual symptoms of schizophrenia, after a promising initial trial. This promises to be a radical breakthrough in addressing a major unmet need in psychiatry: treating negative symptoms of schizophrenia.

Antidepressants

Serendipity played a role in the discovery of the first antidepressant, iproniazid, a monoamine oxidase inhibitor (MAOI) that was used to treat tuberculosis in the 1940s and 1950s; medical staff in sanitariums noticed that the drug elevated the mood of depressed tuberculosis patients. Several other clinically useful MAOIs were then developed (*evolution*).

When the first tricyclic antidepressant (TCA), imipramine, was synthesized, it was intended to be an antipsychotic but—*serendipitously*—turned out to be a strong antidepressant. A *paradigm shift* from MAOIs to TCAs then occurred through the 1970s and 1980s, prompted by concerns over adverse effects caused by the interaction of MAOIs and foods that contain tyramine.

A mechanistic *breakthrough* occurred when the first selective serotonin reuptake inhibitor (SSRI), fluoxetine, was developed in the late 1980s, followed soon by several other SSRIs (*evolution*). This triggered another massive *paradigm shift* away from TCAs to SSRIs because of the low cardiotoxicity of SSRIs.

Evolution then led to the development of other heterocyclic antidepressants, such as nefazodone, mirtazapine, venlafaxine, and duloxetine.

The recent exciting (pun intended again!) discovery of the efficacy of the glutamate NMDA receptor-antagonist ketamine for severe, treatment-resistant depression represents a *radical breakthrough* in the rapidity of remission (within 1 or 2 hours of IV administration) of depression and suicidal impulses. Until now, such rapid response was believed unattainable.

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The ketamine treatment model also represents several *paradigm shifts*: from monoamines to glutamate; from the oral route to the IV route; from gradual (6 to 8 weeks) to abrupt (1 or 2 hours) resolution of symptoms; and from neurochemistry (monoamine neurotransmitters) to neuroplasticity (mammalian target of rapapmycin [mTOR] and brain-derived neurotrophic factor [BDNF]).

The saga will go on

Explosive growth in molecular neuroscience and deeper understanding of the pathophysiology of major psychiatric disorders bode well for an accelerating pace of radical breakthroughs in psychiatric therapies. The new revelation that symptoms of chronic neuropsychiatric disorders such as depression, mania, and schizophrenia can be reversed within a few hours, instead of weeks, months, or years, is jubilant news for our long-suffering patients.

But even as science-driven breakthroughs accelerate and prompt *paradigm shifts* in treatment, we should never underestimate the importance and value of *serendipity* in generating new insights that lead to the same transformative *paradigm shifts* in therapeutics. Scientists are equipped to make discoveries that are breakthroughs, but observant clinicians can make serendipitous discoveries that may reinvent the care of psychotic disorders. The discovery of psychiatric therapies can begin in a clinical setting—not just in the ivory tower of academia.

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References

1. Nasrallah HA, Tandon R. Classic antipsychotic medications. In: Schatzberg AI, Nemeroff CB, eds. Essentials of clinical psychopharmacology, 3rd ed. Arlington, VA: American Psychiatric Publishing Inc.; 2013:219-236.
2. Rosa MA, Lisanby SH. Somatic treatments for mood disorders. Neuropsychopharmacology. 2012;37(1):102-116.
3. Hallak JE, Maia-de-Oliveira JP, Abrao J, et al: Rapid improvement of acute schizophrenia symptoms after intravenous sodium nitroprusside. A randomized, double-blind, placebo-controlled trial. JAMA Psychiatry. 2013; 70(7):668-676.