The serendipity of half a century ago that hatched hoary theories of the etiology of psychopathology is fading rapidly. Transformative models are now emerging to change the landscape of psychiatry.

Nowhere is that change in landscape more apparent than in major depression, the No. 1 disabling condition in all of medicine, according to the World Health Organization. The past decade has generated at least 10 paradigm shifts in the neurobiology and pharmacotherapeutics of depression.

Clinging to simplistic tradition
Most contemporary clinicians continue to practice the traditional model of depression, which is based on the assumption that depression is caused by a deficiency of monoamines: serotonin (5-HT) and norepinephrine (NE). The entire antidepressant armamentarium approved for use by the FDA was designed according to the amine deficiency hypothesis. Depressed patients uniformly receive reuptake inhibitors of 5-HT and NE, but few achieve full remission, as the Sequenced Treatment Alternatives to Relieve Depression (STAR*D) study showed.1

As scientific paradigm shifts infiltrate clinical practice, however, the tired notion of “chemical imbalance” will yield to more complex and evidence-based models. Usually, it would be remarkable to witness a single paradigm shift in the understanding of a brain disorder. Imagine the disruptive impact of multiple scientific shifts within the past decade! Consider the following departures from the old dogma about the simplistic old explanation of depression.

1. From neurotransmitters to neuroplasticity
For half a century, our field tenaciously held to the monoamine theory, which posits that depression is caused by a deficiency of 5-HT or NE, or both. All antidepressants in use today were developed to increase brain monoamines by inhibiting their reuptake at the synaptic cleft. Now, research points to other causes:

- impaired neuroplasticity
- a decrement of neurogenesis
- synaptic deficits
- decreased neurotrophins (such as brain-derived neurotrophic factor)
- dendritic pathology.2,3

2. From ‘chemical imbalance’ to neuroinflammation
The simplistic notion that depression is a chemical imbalance, so to speak, in the brain is giving way to rapidly emerging...
evidence that depression is associated with neuroinflammation. Pro-inflammatory cytokines are elevated in the plasma of depressed patients, and subside when the acute episode is treated. Current antidepressants actually have anti-inflammatory effects that have gone unrecognized. A meta-analysis of the use of anti-inflammatory agents (such as nonsteroidal anti-inflammatory drugs and aspirin) in depression shows promising efficacy. Some inflammatory markers, such as C-reactive protein, already have been reported to predict response to some antidepressants, but not to others.

3. From 5-HT and NE pathways to glutamate NMDA receptors

Recent landmark studies have, taken together, demonstrated that a single IV dose of the N-methyl-D-aspartate (NMDA) receptor antagonist ketamine (a psychotogenic drug of abuse FDA-approved only as an anesthetic) can produce clinical improvement of severe depression and even full remission for several days. Such studies demonstrate that the old dogma of 5-HT and NE deficiency might not be a valid overarching hypothesis of the depression syndrome.

Long-term maintenance studies of ketamine to document its safety and continued efficacy need to be conducted. The mechanism of action of ketamine is believed to be a rapid trigger for enhancing neuroplasticity.

4. From oral to parenteral administration

Several studies have been published showing the efficacy of IV or intranasal administration of new agents for depression. Ketamine studies, for example, were conducted using an IV infusion of a 150-mg dose over 1 hour. Other IV studies used the anticholinergic scopolamine.

Intranasal ketamine also has been shown to be clinically efficacious. Inhalable nitrous oxide (laughing gas, an NMDA antagonist) recently was reported to improve depression as well.

It is possible that parenteral administration of antidepressant agents may exert a different neurobiological effect and provide a more rapid response than oral medication.

5. From delayed efficacy (weeks) to immediate onset (1 or 2 hours)

The widely entrenched notion that depression takes several weeks to improve with an antidepressant has collapsed with emerging evidence that symptoms of the disorder (even suicidal ideation) can be reversed within 1 or 2 hours. IV ketamine isn’t the only example; IV scopolamine, inhalable nitrous oxide, and overnight sleep deprivation also exert a rapid therapeutic effect. This is a major rethinking of how quickly the curtain of severe depression can be lifted, and is great news for patients and their family.

6. From psychological symptoms to cortical or subcortical changes

Depression traditionally has been recognized as a clinical syndrome of sadness, self-deprecation, cognitive dulling, and vegetative symptoms. In recent studies, however, researchers report that low hippocampus volume in healthy young girls predicts future depression. Patients with unremitting depression have been reported to have an abnormally shaped hippocampus.

In addition, gray-matter volume in the subgenual anterior cingulate (Brodmann area 24) is hypoplastic in depressed persons, making that area a target for deep-brain stimulation (DBS). Brain morphological changes such as a hypoplastic hippocampus might

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become useful biomarkers for identifying persons at risk of severe depression, and might become a useful adjunctive biomarker for making a clinical diagnosis.

7. From healing the mind to repairing the brain
It is well-established that depression is associated with loss of dendritic spines and arborizations, loss of synapses, and diminishment of glial cells, especially in the hippocampus and anterior cingulate. Treating depression, whether pharmaceutical or somatic, involves reversing these changes by increasing neurotrophic factors, enhancing neurogenesis and gliogenesis, and restoring synaptic and dendritic health and cell survival in the hippocampus and frontal cortex.

8. From pharmacotherapy to neuromodulation
Although drugs remain the predominant treatment modality for depression, there is palpable escalation in the use of neuromodulation methods.

The oldest of these neuromodulatory techniques is electroconvulsive therapy, an excellent treatment for severe depression (and one that enhances hippocampal neurogenesis). In addition, several novel neuromodulation methods have been approved (transcranial magnetic stimulation and vagus nerve stimulation) or are in development (transcranial direct-current stimulation, cranial electrotherapy stimulation, and DBS). These somatic approaches to treating the brain directly to alleviate depression target regions involved in depression and reduce the needless risks associated with exposing other organ systems to a drug.

9. From monotherapy to combination therapy
The use of combination therapy for depression has escalated with FDA approval of adjunctive use of atypical antipsychotics in unipolar and bipolar depression. In addition, the landmark STAR*D study demonstrated the value of augmentation therapy with a second antidepressant when 1 agent fails. Other controlled studies have shown that combining 2 antidepressants is superior to administering 1.

Just as other serious medical disorders—such as cancer and hypertension—are treated with 2 or 3 medications, severe depression might require a similar strategy. The field gradually is adopting that approach.

10. From cortical folds to wrinkles on the face
Last, a new (and unexpected) paradigm shift recently emerged, which is genuinely intriguing—even baffling. Using placebo-controlled designs, several researchers have reported significant, persistent improvement of depressive symptoms after injection of onabotulinumtoxinA in the corrugator muscles of the glabellar region of the face, where the omega sign often appears in a depressed person.

The longest of the studies was 6 months; investigators reported that improvement continued even after the effect of the botulinum toxin on the omega sign wore off. The proposed mechanism of action is the facial feedback hypothesis, which suggests that, biologically, facial expression has an impact on one’s emotional state.

Big payoffs coming from research in neuroscience
These 10 paradigm shifts in a single psychiatric syndrome are emblematic of exciting clinical and research advances.
in our field. Like all syndromes, depression is associated with multiple genetic and environmental causes; it isn’t surprising that myriad treatment approaches are emerging.

The days of clinging to monolithic, serendipity-generated models surely are over. Evidence-based psychiatric brain research is shattering aging dogmas that have, for decades, stifled innovation in psychiatric therapeutics that is now moving in novel directions.

Take note, however, that the only paradigm shift that matters to depressed patients is the one that transcends mere control of their symptoms and restores their wellness, functional capacity, and quality of life. With the explosive momentum of neuroscience discovery, psychiatry is, at last, poised to deliver—in splendid, even seismic, fashion.  

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References

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