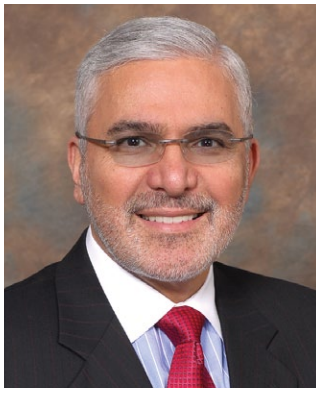

Henry A. Nasrallah, MD
Editor-in-Chief

The hazards of serendipity

For many scientists and clinicians, serendipity is a welcome blessing. It can result in the fortuitous discovery of a new treatment for a previously untreatable illness. In psychiatry, there are several examples, including chlorpromazine for psychosis and monoamine oxidase inhibitors and tricyclics for depression. But serendipity also can have a downside. It can skew and misdirect research efforts into one direction to the exclusion of others, which can be a curse in the pursuit of scientific truth.

Novel mechanisms and therapeutic targets for depression are emerging via basic neuroscience research, not happenstance

For example, consider major depressive disorder (MDD), which is a major public health challenge with enormous direct and indirect costs to society. MDD is the most disabling medical disorder not just in psychiatry, but in the entire field of medicine (psychiatry claims 3 other disorders in the top 5: schizophrenia, bipolar disorder, and alcohol abuse).[1] In the United States, 8% to 10% of the population—children, adolescents, adults, and geriatric patients—suffer from depression at some point in their lives, and many will attempt suicide or die from self-inflicted injury if their depression is left untreated.[2] In the United States, 34,000 persons die each year from suicide[3]; most of them have MDD.[4]

Despite the gravity of depression's disabling effects, MDD treatment barely has budged from the entrenched model constructed around increasing the availability of ≥1 monoamines—serotonin, norepinephrine, and dopamine—in the brain. For the past 5 decades, researchers have not deviated from the therapeutic dogma spawned by serendipity. Yet the efficacy of antidepressants from tricyclics to selective serotonin reuptake inhibitors to serotonin-norepinephrine reuptake inhibitors has been less than stellar, with remission in a few patients, partial response in others, and treatment resistance in many.

This is not surprising given that depression is a diverse syndrome, a heterogeneous gamut of disorders with variable pathogenesis but a shared clinical phenotype. So why did the pharmaceutical industry continue to develop drugs that inhibit the reuptake of one monoamine or another instead of innovating and developing novel agents with diverse mechanisms of action? Powerful inertia of the serendipitously discovered older antidepressants has persisted, without the benefit of new, "out-of-the-monoamine-box" innovative discovery based on emerging pathophysiologic research in mood disorders.

Things finally may be changing. Basic neuroscience and animal models have generated a wealth of new mechanisms and pathways that seem to work in animal models of depression, such as learned helplessness and social defeat.[5] The old mold of monoamine reuptake inhibition soon may

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be replaced by a plethora of alternatives that may transform the landscape of depression treatment.

Emerging therapeutic targets

Consider the following novel mechanisms that may become the basis for creating entirely new antidepressants in the foreseeable future, by design, not by serendipity:

- corticotropin-releasing factor (CRF) and glucocorticoids
  - CRF antagonists
  - vasopressin receptor antagonists
  - glucocorticoids as agonists or antagonists
- neurokinin system
- brain derived neurotropic factor (BDNF) and other neurotropins, such as fibroblast growth factor (FGF) or vascular endothelial growth factor (VEGF)
- phosphodiesterase inhibitors
- glutamate pathway modulators
  - ketamine (IV infusion with immediate efficacy)
  - α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic (AMPA) receptor modulators
  - glycine
- hypothalamic feeding peptides
- circadian gene products
- other evolving antidepressants
  - K-opioid receptor antagonists
  - CB_1 cannabinoid receptor agonists/antagonists
  - cytokines
  - melatonin receptor agonists
  - galanin
  - neuropeptide Y
  - histone deacetylase inhibitors
  - tissue plasminogen activator

It is heartening to psychiatrists and their chronically depressed patients that many novel mechanisms and therapeutic targets have emerged, thanks to intensive research, not serendipity and happenstance. Although that's uplifting news, the sobering downside is the lack of sufficient resources to expedite translational research. We need far more funding than what is available, and several pharmaceutical companies have dismantled their psychiatry research infrastructure and laid off thousands of scientists. This may be the time when strong philanthropic support may have to come to the rescue of this worthy cause, similar to how the Bill & Melinda Gates Foundation has focused on eradicating malaria. If only a multi-billionaire would adopt depression research as his or her pet charity with the goal of discovering several effective new treatments for the most disabling medical disorder in the world. What a fantastic legacy that would be.

Serendipity is out, intensive (and expensive!) brain research is in! Calling all enlightened billionaires…

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