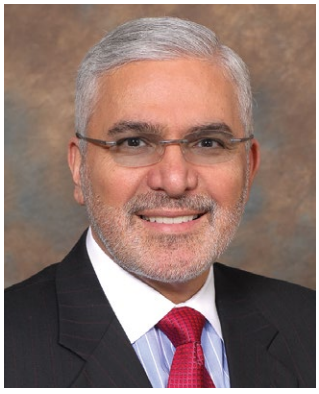

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Reversing depression: A plethora of therapeutic strategies and mechanisms

Despite much progress, major depressive disorder (MDD) continues to be a challenging and life-threatening neuropsychiatric disorder. It is highly prevalent and afflicts tens of millions of Americans.

It is also ranked as the No. 1 disabling medical (not just psychiatric) condition by the World Health Organization.[1] A significant proportion of patients with MDD do not respond adequately to several rounds of antidepressant medications,[2] and many are labeled as having "treatment-resistant depression" (TRD).

In a previous article, I provocatively proposed that TRD is a myth.[3] What I meant is that in a heterogeneous syndrome such as depression, failure to respond to 1, 2, or even 3 antidepressants should not imply TRD, because there is a "right treatment" that has not yet been identified for a given depressed patient. Most of those labeled as TRD have simply not *yet* received the pharmacotherapy or somatic therapy with the requisite mechanism of action for their variant of depression within a heterogeneous syndrome. IV ketamine, which, astonishingly, often reverses severe TRD of chronic duration within a few hours, is a prime example of why the term TRD is often used prematurely. Ketamine's mechanism of action (immediate neuroplasticity via glutamate *N*-methyl-D-aspartate receptor antagonism, and stimulation of the mammalian target of rapamycin [mTOR]) was not recognized for decades because of the obsession with the monoamine model of depression.

Some clinicians may not be aware of the abundance of mechanisms of action currently available for the treatment of MDD as well as bipolar depression. Many practitioners, in both psychiatry and primary care, usually start the treatment of depression with a selective serotonin reuptake inhibitor, and if that does not produce a response or remission, they might switch to a serotonin-norepinephrine reuptake inhibitor. If that does not control the patient's depressive symptoms, they start entertaining the notion that the patient may have TRD, not realizing that they have barely scratched the surface of the many therapeutic options and mechanisms of action, one of which could be the "best match" for a given patient.[4]

There will come a day when "precision psychiatry" finally arrives, and specific biomarkers will be developed to identify the "right" treatment for each patient within the heterogenous syndrome of depression.[5] Until that day arrives, the treatment of depression will continue to be a process of trial and error, and hit or miss. But research

Some clinicians may not be aware of the abundance of mechanisms of action available for treating MDD

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Table

Currently available treatments for depression

FDA-approved pharmacotherapies[6]
- Selective serotonin reuptake inhibitor (**SSRI**) (eg, fluoxetine, sertraline)
- Norepinephrine-dopamine reuptake inhibitor (**NDRI**) (eg, bupropion)
- Serotonin-norepinephrine reuptake inhibitor (**SNRI**) (eg, venlafaxine, duloxetine)
- Serotonin-2 antagonists/reuptake inhibitor (**SARI**) (eg, trazodone, nefazodone)
- Serotonin-1A partial antagonist/ serotonin reuptake inhibitor (**SPARI**) (eg, vilazodone)
- Serotonin modulator and stimulator (**SMS**) (eg, vortioxetine)
- Presynaptic alpha-2 receptor antagonist (**PARA**) (eg, mirtazapine)
- Nonselective cyclic antidepressant (**NCA**) (eg, amitriptyline, desipramine)
- Irreversible monoamine oxidase (A & B) inhibitor (**MAOI**) (eg, phenelzine)
- Reversible inhibitor of MAO-A (**RIMA**) (eg, moclobemide)
- Irreversible MAO-B inhibitor (eg, selegiline)
- NMDA receptor antagonist (eg, esketamine, dextromethorphan)
- GABA-A receptor antagonist (eg, brexanolone)

Nonapproved pharmacotherapies (with published studies)
- Buprenorphine
- Onabotulinum A
- mTOR stimulator
- Scopolamine IV
- Ketamine IV
- Psilocybin
- Armodafinil

FDA-approved neuromodulation therapies
- Electroconvulsive therapy (**ECT**)
- Vagus nerve stimulation (**VNS**)
- Repetitive transcranial magnetic stimulation (**rTMS**)

Nonapproved neuromodulation therapies
- Trigeminal nerve stimulation (**TNS**)
- Deep brain stimulation (**DBS**)

Somatic and other antidepressant therapies
- Sleep deprivation (temporary but dramatic)
- Ultrabright light
- Exercise
- Cognitive-behavioral therapy (**CBT**)

Adjunctive therapies
- Aripiprazole
- Quetiapine
- Brexpiprazole
- Cariprazine
- Lithium
- Deplin
- Thyroid hormones (T2 and T4)

Monotherapies for bipolar depression
- Quetiapine
- Lurasidone
- Cariprazine
- Lumateperone

Combination therapy for bipolar depression
- Olanzapine-fluoxetine combination (**OFC**)

GABA: gamma-aminobutyric acid; mTOR: mammalian target of rapamycin; NMDA: *N*-methyl-D-aspartate

will eventually discover genetic, neurochemical, neurophysiological, neuroimaging, or neuroimmune biomarkers that will rapidly guide clinicians to the correct treatment. This is critical to avoid inordinate delays in achieving remission and avert the ever-present risk of suicidal behavior.

The ***Table***[6] provides an overview of the numerous treatments currently available to manage depression. All increase brain-derived neurotrophic factor and restore healthy neuroplasticity and neurogenesis, which are impaired in MDD and currently believed to be a final common pathway for all depression treatments.[7]

These 41 therapeutic approaches to treating MDD or bipolar depression reflect the heterogeneity of mechanisms of action to address an equally heterogeneous syndrome. This implies that clinicians have a wide array of on-label options to manage

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One of the exciting new discoveries is psilocybin, which increases the brain's network flexibility and alters the dark mental perspective of depression

patients with depression, aiming for remission, not just a good response, which typically is defined as a ≥50% reduction in total score on one of the validated rating scales used to quantify depression severity, such as the Montgomery-Åsberg Depression Rating Scale, Hamilton Depression Rating Scale, or Calgary Depression Scale for Schizophrenia.

When several FDA-approved pharmacotherapies fall short and produce a suboptimal response, clinicians can resort to other treatment options known to have a higher efficacy than oral antidepressants. These include electroconvulsive therapy, repetitive transcranial magnetic stimulation, and vagus nerve stimulation. Other on-label options include adjunctive therapy with one of the approved second-generation antipsychotic agents or with adjunctive esketamine.

But if the patient still does not improve, one of many emerging off-label treatment options may work. One of the exciting new discoveries is the hallucinogen psilocybin, whose mechanism of action is truly unique. Unlike standard antidepressant medications, which modulate neurotransmitters, psilocybin increases the brain's network flexibility, decreases the modularity of several key brain networks (especially the default-brain network, or DMN), and alters the dark and distorted mental perspective of depression to a much healthier and optimistic outlook about the self and the world.[8] Such novel breakthroughs in the treatment of severe depression will shed some unprecedented insights into the core neurobiology of depression, and may lead to early intervention and prevention.

As the saying goes, all roads lead to Rome. Psychiatric clinicians should rejoice that there are abundant approaches and therapeutic mechanisms to relieve their severely melancholic (and often suicidal) patients from the grips of this disabling and life-altering brain syndrome.

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