Factors That Predispose Patients to Treatment-Resistant Depression

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What to do once treatment-resistant depression is established based on risk factors and exclusion of other conditions? Insights here—and a treatment algorithm.

Decades of research have focused on the identification of risk factors associated with treatment-resistant depression (TRD). The most reliable include:

- Duration of the episode: the longer the episode of depression, the greater the atrophy in specific brain regions (eg, hippocampus); the cognitive and behavioral changes that take place during long episodes make a return to previous well-being difficult
- Severity of the episode: both ends of the depression spectrum (most severe, mildest) are hypothesized to increase the risk of poor response—severe depression is associated with biological unbalances; mild depression, with lower drug versus placebo response
- Melancholic features: TRD is more prevalent in bipolar depression than in MDD; the specific investigation of subthreshold manic symptoms is pivotal
- Lack of symptomatic improvement within the first couple of weeks since the start of treatment
- Comorbidity: anxious symptoms and full anxiety disorders (especially generalized anxiety disorder) were found to be predictors of lower rates of response and remission; personality disorders, especially avoidant and borderline, are negative prognostic factors
- Old age

Biological factors have also been studied as possible predictors of TRD. Genetic variants within the serotonin transporter—serotonin receptors and genes involved in neurodevelopment—have been found to modulate the risk of TRD. Although this very promising predictive tool is still under development, a number of research centers worldwide are currently using gene-targeted antidepressant prescription (eg, the Canadian Centre for Addiction and Mental Health Pharmacogenetics Program). A further development is the identification of peripheral blood biomarkers or imaging predictors.

Before treating TRD, however, due diligence is advised. A number of conditions are possible causes of relative or “pseudo” TRD:

- Subtherapeutic doses of antidepressants (approximately 20%)
- Patient nonadherence (approximately 40%)
- Intolerable adverse effects (20% to 30%)
- Wrong diagnosis (10% to 15%) (such as, thyroid disease, nutritional deficiencies, sleep apnea, “latent” bipolarity)

Treatment options

Once TRD is established on the basis of one or more of the risk factors and the exclusion of other conditions, the question arises: what to do next? Unfortunately the answer is not clear, but a number of options are available. The Figure presents a treatment algorithm for TRD.

A combination of 2 antidepressants or augmentation with another drug, such as lithium, a thyroid hormone, or an atypical antipsychotic, can be tried. The most robust evidence is augmentation of conventional antidepressant therapy with atypical antipsychotics. Switching to another antidepressant may also help. However, there is no clear evidence to guide the choice between augmentation and switching. Clinical experience and preliminary scientific evidence support the option of augmenting when partial symptomatic improvement is observed during the current antidepressant treatment.

Vortioxetine is an FDA-approved pharmacological option for the treatment of MDD. It is a serotonin modulator and stimulator that blocks the serotonin transporter, a partial agonist of serotonin receptor 1B and antagonist of serotonin receptors 3A and 7. Vortioxetine demonstrated good tolerability and a beneficial effect on cognition that appears largely independent from the effect on depressive symptoms.
The combination of antidepressant pharmacotherapy and psychotherapy (usually cognitive-behavioral therapy) is an effective option; however, the cost-effectiveness of this strategy has not been evaluated. Other nonpharmacological treatments have been widely studied. The use of light therapy, possibly in combination with physical exercise, has demonstrated a considerable antidepressant and anxiolytic effect. Neurostimulation represents a more invasive option that can be helpful in highly refractory patients. Repetitive transcranial magnetic stimulation (rTMS) provided promising results in the treatment of TRD after 2 or more antidepressant treatment trials failed. Moreover, rTMS reduced cognitive impairment and improved patient acceptability compared with electroconvulsive therapy. Vagus nerve stimulation was shown to be effective in chronic TRD, with a 12-month response of 30% or more. The evidence for deep brain stimulation is compelling as a promising but still experimental treatment strategy in highly resistant patients. Findings indicate a response rate of 40% to 70%. Ketamine has gained particular interest because of its marked and immediate antidepressant action (substantial improvement is evident within 24 hours). Ketamine has also been found to be effective in severe TRD and bipolar depression. However, ketamine tolerability is poor, especially for dissociative symptoms, which commonly emerge. Intranasal administration of ketamine has demonstrated rapid antidepressant effects that appeared comparable to those achieved with the intravenous route but with minimal adverse effects. Despite the possible benefits of this novel approach, a major issue with ketamine is its brief antidepressant effect, which lasts no more than a few days, even with repeated administrations. A number of studies are under way worldwide to identify compounds that are similar to ketamine in the manner in which they target the N-methyl-aspartate receptor but with acceptable tolerability and persistence of effect. Other antidepressants with an innovative mechanism of action are those modulating the inflammatory-immune system. Besides augmentation with NSAIDs such as celecoxib, the tumor necrosis factor antagonist infliximab was recently suggested as another possible effective option for patients with increased C-reactive protein concentration at baseline. The evidence for the use of molecules with stimulant-like properties is ambiguous. The most compelling evidence available is for lisdexamfetamine as augmentation to escitalopram. The effect of this combination was estimated to be similar to that obtained through atypical antipsychotic augmentation.

A more conservative line of research is the development of multitarget monoamine antidepressants. Triple monoamine uptake blockers were developed with the idea of directly modifying different symptomatic domains of MDD, including anhedonia (hypothesized to be a consequence of dopaminergic deficits). A nicotinic acetylcholine receptor agonist and triple monoamine uptake blocker is a further evolution that demonstrated procognitive effect besides antidepressant-like and anxiolytic-like effects in preclinical studies.

CASE VIGNETTE

Emma is 67 years old with major depression. Her first major depressive episode occurred when she was 23; she was given amitriptyline and had rapid symptom resolution. She was well until age 56, when the depression recurred after a stressful event. Symptom remission followed 2 months of treatment with 40 mg/d of amitriptyline and 600 mg/d of lithium.

After receiving maintenance treatment and being healthy for 4 years, her depression returned after the death of a close relative. Emma was hospitalized and treated with 20 mg/d of citalopram for 4 weeks without symptom improvement. A switch to 70 mg/d of amitriptyline with lithium augmentation (600 mg/d) allowed a relevant improvement. After 8 months, treatment with amitriptyline and lithium was suspended and 100 mg/d of fluvoxamine was introduced as maintenance therapy. However, because of GI adverse effects, Emma stopped taking the fluvoxamine.

She missed follow-up visits but returned after 7 months, complaining of depressed mood, loss of interest, psychomotor retardation, social withdrawal, feelings of guilt, anxiety, and suicidal ideation. She received 100 mg/d of amitriptyline and 600 mg/d of lithium. After 1 month, the depressive symptoms had not improved; thus, amitriptyline was titrated to 125 mg/d. Symptoms persisted and she was hospitalized after another month. She was given 200 mg/d of fluvoxamine.

Symptom improvement was seen at discharge, but Emma complained about the persistence of inner suffering. She saw her general practitioner, who prescribed 100 mg/d of clomipramine and 600 mg/d of lithium; after 2 months, symptoms persisted. Soon after, she presented to the emergency department complaining of depression and suicidal ideation and was hospitalized. She received 300 mg/d of venlafaxine for 7 weeks, with no symptom improvement; thus, treatment with amitriptyline, 60 mg/d, was restarted, and she was discharged after mild improvement. During follow-up,
amitriptyline was increased to 150 mg/d and 600 mg/d of lithium was added; a few days later, the patient attempted suicide. During the following hospitalization, Emma was treated with 160 mg/d of amitriptyline, 600 mg/d of lithium, and 50 μg/d of levothyroxine, resulting in slow but complete symptom remission.

Emma’s case is emblematic of melancholic recurrent MDD with a selective response to the antidepressant amitriptyline, which blocks the serotonin transporter and has a lower affinity for the noradrenaline transporter than other TCAs. Several attempts of replacing amitriptyline with better-tolerated antidepressants (citalopram, fluvoxamine, venlafaxine) failed, possibly because of their selectivity for the serotonin transporter or the noradrenaline transporter. On the other hand, clomipramine was not effective, possibly because of its highly prevalent serotonergic activity compared with amitriptyline. The lack of efficacy of these antidepressants was accompanied by reduced treatment adherence.

CASE VIGNETTE
Julia is 75 years old. The first episode of depression occurred when she was 47—after a major life event. During that time, she began using alcohol with detrimental social and occupational consequences. The alcohol-related disorder remitted 8 years later, but during that period, Julia experienced depressive mood, loss of interest, social withdrawal, and insomnia. She was treated with several TCAs (clomipramine, imipramine, amitriptyline) without clinical benefit. Partial improvement was seen after a year, but without her previous level of functioning. After another major life event at age 57, she again became severely depressed with psychomotor retardation, appetite and weight loss, psychic and somatic anxiety, feelings of guilt, and suicidal ideation. Treatment was started with 75 mg/d of amitriptyline, titrated to 125 mg/d, with 600 mg/d of lithium augmentation. After symptoms remitted, amitriptyline was reduced to 25 mg/d. But several months later, mild depressive symptoms recurred and did not improve after an increase to 75 mg/d of amitriptyline. A switch to 50 mg/d of nortriptyline was made; however, an increase of anxiety required a return to 50 mg/d of amitriptyline. Symptom remission occurred a few months later.

Julia had 2 more episodes of depression in her late 60s. Both were treated with 300 mg/d of fluvoxamine, with response within 4 weeks. She was well on fluvoxamine (100 mg/d) maintenance therapy until age 73, when she was hospitalized after another depressive episode. An increase in fluvoxamine to 200 mg/d provided slow improvement and eventual symptom remission. After discharge, there was rapid recurrence of depressive symptoms with marked anxiety. Trials of mirtazapine 30 mg/d and clomipramine 20 mg/d provided poor clinical benefits. There were 4 further hospitalizations, with rapid recurrence of symptoms after initial improvement with various combinations of psychotropics. During the last hospitalization, 90 mg/d of amitriptyline was augmented with 1 mg/d of risperidone, which resulted in mood and anxiety improvement but with episodes of disorientation and confusion. Amitriptyline was replaced with 10 mg/d of escitalopram, with initial improvement.

Julia has a severe form of recurrent MDD, with a middle-age onset that occurred after a stressful life event. Later episodes developed without external events. Amitriptyline was most effective throughout illness, but it was not tolerated as she grew older because of the emergence of anticholinergic adverse effects. Old age, long duration of an episode, and anxiety symptoms were all present and contributed to TRD. The combination of escitalopram and risperidone was appropriate given the marked anxiety that characterized the last phase of the disease.
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Disclosures:
Dr Serretti is Associate Professor and Dr Fabbri is a Resident in the department of biomedical and neuromotor sciences at the Institute of Psychiatry, University of Bologna, Bologna, Italy. They report no conflicts of interest concerning the subject matter of this article.

References:


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