When the glass is always half empty

There is no one-size-fits-all approach to managing treatment-resistant depression, experts tell **Melinda Wenner Moyer**

When Juan Rivera was in college, he noticed that the activities he loved, such as going out with friends, had stopped making him happy.

"I would be with my friends but not enjoying it fully and just sort of feeling flat," he said. On bad days, he could barely get out of bed, much less summon the motivation to leave the house.

Rivera, now 35, discussed his struggles with a psychiatrist. She evaluated him, diagnosed him with depression and prescribed an antidepressant.

It didn't work. Over the next few years, she prescribed several others but those didn't help him, either.

Rivera, an immigration attorney in Miami, US, suffers from what most clinicians would call "treatment-resistant depression". There is no broadly accepted definition of the condition and there can be various degrees of treatment resistance, said Dr Gerard Sanacora, director of the Yale Depression Research Program, US. But many doctors, he said, consider depression to be treatment-resistant if a person has not experienced at least a 50 per cent improvement after trying two different antidepressants in succession, each for four to six weeks.

Despite its name, treatment-resistant depression can improve and even be cured. A number of therapies, often in combination, have been shown to help.

Various factors may increase the likelihood that a person with depression won't respond to initial drug treatments, said Dr Debra Kahn, director of the Advanced Psychiatric Therapeutics Clinic at UC Davis Health, US.

People with a history of childhood trauma can experience depression that is more difficult to treat. When those with depression also have anxiety, certain vitamin deficiencies, thyroid disease, heart disease or sleep apnoea, they may also struggle to improve, in part because these conditions can cause depression-like symptoms such as fatigue, Dr Kahn said.

Genetic differences may also shape the likelihood that depression will become treatment-resistant, Dr Kahn added. A 2025 study reported that genetic predispositions to insomnia and certain forms of neuroticism increase the risk.

A person's expectations may also shape outcomes. If someone has tried several medications without improving, that person may understandably not expect much from the next one, Dr Sanacora said.

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> A therapy that has been shown to help is transcranial magnetic stimulation or TMS. It uses magnetic pulses to stimulate the brain to release mood-boosting chemicals

An estimated 31 per cent of people in the US who are treated for depression are considered treatment resistant, according to a 2021 study. And there is no one-size-fits-all approach to managing treatment-resistant depression.

At the UC Davis clinic, if patients don't improve after trying two antidepressants in succession and undergoing psychotherapy, they may be prescribed a low dose of an additional drug such as an atypical antipsychotic or lithium, Dr Kahn said. Clinicians will ensure that medical problems that could be contributing to symptoms are addressed, too.

One additional therapy that has been shown to help people with treatment-resistant depression is transcranial magnetic stimulation or TMS, which was cleared by the US Food and Drug Administration to treat depression in 2008, Dr Kahn said. It uses magnetic pulses to stimulate parts of the brain to release mood-boosting chemicals including norepinephrine, dopamine and serotonin. TMS is tolerated well and has no long-term serious side effects.

A 2023 meta-analysis of 19 clinical trials found that patients who received TMS while taking an antidepressant were 2.8 times as likely to experience remission compared with people who took an antidepressant while receiving a sham TMS treatment as a placebo.

Ketamine, an anaesthetic commonly used in surgery, is increasingly used to address treatment-resistant depression. In 2019, the FDA approved Spravato, an intranasal spray containing esketamine. In a 2019 trial, 52.5 per cent of patients with treatment-resistant depression who took esketamine with an antidepressant for 28 days experienced a significant resolution of their symptoms compared with about 31 per cent of people who took an antidepressant with a placebo.

Ketamine is thought to work in part by helping the brain form new or stronger connections in networks involved in mood and cognition, Dr Kahn said. Psychedelic medicines including psilocybin, ibogaine and 5-MeO-DMT, which are thought to work in similar ways, are also being studied as potential treatments.

Rivera recently began taking intranasal Spravato and he started feeling better after his second session. The medication is helping lift the "negative filter", he said, that permeates his thoughts and mood.

That said, there is unlikely to be one "magic pill" that cures treatment-resistant depression. People may benefit from a combination of approaches and may also need lifestyle changes.

Dr Sanacora always asks his patients what they plan to do over the upcoming weekend to ensure they're active and seeking out joy. "You can take the medicine but you also have to do the other physical and social interventions that are so important," he said.

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