Depression seems to be getting much harder to treat – or is it?

Maybe we misunderstood the condition, says Samantha Murphy, and we already have the key to a better cure

One of Vanessa Price’s first chronic cases was a woman we’ll call Paula. Paula came to the London Psychiatry Centre, where she was a registered nurse, after two years of unrelenting depression. First she stopped seeing her friends. Then she stopped getting out of bed. Finally, she began cutting herself. Neither sessions with a psychiatrist nor medications helped. In fact, they made it worse. Paula joined the ranks of people diagnosed with treatment-resistant depression.

The steady rise of this diagnosis over the past two decades reflects a little-known trend. The effectiveness of antidepressant drugs has been overstated – so much so that some pharmaceutical companies have been driven out of developing them altogether.

The stubborn nature of these cases of depression has, however, spurred research into new and sometimes unorthodox treatments of last resort. Their surprising and impressive results suggest that there has been a fundamental problem in our understanding of the disorder.

In fact, the new research has opened the door to thinking about depression not as a single condition but a continuum of illnesses, all with different underlying neurological mechanisms – which may hold clues to lasting relief. This promise has sparked a renaissance in drug development not seen since the 1950s.

Depression is a disease whose brutality is only matched by its perverseness. Many trials linked depression to low serotonin levels, which were thought to disrupt the brain’s ability to pass messages across synapses, the tiny gaps between neurons.

What causes people to become clinically depressed? The dominant theory is that depression results from a chemical imbalance in the brain, with a neurotransmitter called serotonin usually implicated as the prime suspect. Many trials linked depression to low levels of it, which were thought to disrupt the brain’s ability to pass messages across synapses, the tiny gaps between neurons.

Mysterious decline

Find a way to boost serotonin, the thinking went, and both neural signalling and mood would return to normal. The first drug based on the serotonin hypothesis – fluoxetine, better known as Prozac – was launched in the late 1980s, and nearly all subsequent antidepressants have operated on the same general principle: keep levels of serotonin high by preventing the brain from reabsorbing and recycling it.

Though such drugs remain the go-to tools for lifting depression, however, they seem to be getting less effective (see “False dawn”, p 36). Clinical trials in the 1980s and 1990s indicated that these drugs would help 60 to 70 per cent of depressed people go into remission. But studies in the 2000s showed that standard antidepressants work only in 60 to 70 per cent of people, a decline that was underscored in 2006 when the National Institute of Mental Health (NIMH) in Bethesda, Maryland published the results of a massive, nationwide clinical trial. Unlike many pharmaceutical trials – which often screen out certain participants – this was the first to measure the effectiveness of antidepressants in a population representative of the real world. The results were disquieting: few of the 2876 participants fully recovered without switching to or in many cases adding other medications.

What can explain this apparent decline in the potency of antidepressants? Perhaps the drugs themselves were never quite as effective as claimed. To approve a given antidepressant, the US Food and Drug Administration only requires two large-scale studies to verify that the drug is superior to a placebo. However, pharmaceutical companies are under no obligation to supply the FDA with every study they have conducted, only the positive ones.

When David Mischoulon, director of psychiatry research at Massachusetts General Hospital in Boston, sifted through previously unpublished data from pharmaceutical trials, he says he found many more negative results than positive ones. A high percentage of studies showed that the placebo was just as effective as claimed. “Now we think it’s more in the reflection of the time it took doctors to see that the placebo was just as good,” Mischoulon says. The rise of treatment-resistant depression, then, might have been a reflection of the time it took doctors to see that reality reflected in their clinical practice.

Could the failure of the drugs be down to a problem in our understanding of the underlying mechanisms? After all, untreatable depression wasn’t the only inconsistency to
Instead of enabling a broken brain to pass on messages, glutamate may be teaching the brain how to rebuild itself

It wasn’t that she wanted to die, she says; she felt like a failure,” Paula says. After nothing worked, she was surprised to find herself enjoying it. “That would have been unthinkable before,” she says. But that’s where the similarity ends. Rather than simply aiding in the transport of messages from neurons, glutamate may be a factor in helping the brain’s neurons repair themselves. This would dovetail with a theory of depression known as structural changes in the brain, which says that in people predisposed to recurring depression, ketamine may help neurons permanently maintain new and this might explain why people can respond to ketamine in different ways. One example is GLYX-13, which showed promise in preclinical trials earlier this year. AstraZeneca, Roche and Janssen, among others, are also developing drugs not as a last-resort treatment for depression, but for first-line use. One tantalising possibility remains. If so, how will individuals know which type of ketamine they have? One way to find out would be to see which drugs are effective. “If you don’t get a response from ketamine the first day, you probably won’t,” says Zarate. Work to develop a diagnostic test is already under way. “We’re trying to identify certain factors in the blood associated with certain subtypes of depression,” says Mischoulon. Brain scans are another possibility: these can already show whether depression will respond better to talk therapy or medication.

All this research is still very much in its infancy, but well before bio-marker tests arrive, there should be a raft of new medications that exploit glutamate to combat depression. At least five companies have been working on ketamine derivatives without the cognitive effects that led to the drug’s enthusiastic recreational use. One example is GSK, which showed promise in preclinical trials which showed promise in preclinical trials earlier this year. AstraZeneca, Roche and Janssen, among others, are also developing both pills and intravenous drugs, the first of which should be with us within a couple of years. While some pharmaceutical companies are even focusing on glutamate drugs not as a last-resort treatment for depression, but for first-line use. One tantalising possibility remains. If so, how will individuals know which type of ketamine they have? One way to find out would be to see which drugs are effective. “If you don’t get a response from ketamine the first day, you probably won’t,” says Zarate. Work to develop a diagnostic test is already under way. “We’re trying to identify certain factors in the blood associated with certain subtypes of depression,” says Mischoulon. Brain scans are another possibility: these can already show whether depression will respond better to talk therapy or medication.

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