Drugmakers target depression’s cognitive fog

Industry and researchers push for ways to assess memory and concentration deficits.

By Heidi Ledford

In the past quarter of a century, a wave of drugs has transformed the treatment of depression. But the advances have struggled to come to grips with symptoms that often linger long after people start to feel better: cognitive problems such as memory loss and trouble concentrating.

On 3 February, the US Food and Drug Administration (FDA) will convene a meeting of its scientific advisers to discuss whether such cognitive impairments are components of the disorder that drugs might be able to target — or just a result of depressed mood. The discussion will help the agency to decide whether two companies that sell the antidepressant vortioxetine should be allowed to label it as a treatment for the cognitive effects. A ‘yes’ could spur drug developers to invest in ways to test cognitive function during their antidepressant trials.

Psychiatrists have long noted that some people with depression also struggle to concentrate and to make decisions. The question has been whether such difficulties are merely an offshoot of altered mood and would thus clear up without specific treatment, says Diego Pizzagalli, a neuroscientist at McLean Hospital, an affiliate of Harvard Medical School in Belmont, Massachusetts.

But some patients who report improved mood after treatment still struggle with cognitive deficits — so psychiatrists sometimes prescribe concentration-enhancing drugs that are approved to treat attention deficit hyperactivity disorder to people with depression.

The scenario is a familiar one for those who treat schizophrenia: antipsychotic drugs may drive away hallucinations, but the cognitive deficits persist. And the deficits make it difficult for people with schizophrenia to keep jobs or to live independently, says Michael Green, a neuropsychologist at the University of California, Los Angeles.

Long lead time

More than a decade ago, companies waged a campaign to encourage drug regulators to recognize cognitive impairment in schizophrenia. But the FDA refused to do so until drugmakers came up with uniform criteria to measure the impairments. As a result, the schizophrenia community built a consensus around a battery of tests for use in clinical trials. In the case of depression, tests would have to be especially sensitive because the cognitive impairments can be more subtle than those that accompany schizophrenia, says Richard Keefe of the Duke Institute for Brain Sciences in Durham, North Carolina.

Researchers and industry representatives discussed the problem of cognitive impairment in depression at a workshop held by the US Institute of Medicine (now the National Academy of Medicine) almost a year ago, but they did not set a
course for establishing uniform assays. And even if tests acceptable to the FDA can be established, that is no guarantee that effective drugs will soon follow. Guidelines governing schizophrenia trials were established in 2005, but no cognitive-function drug has yet been approved in such cases. Furthest along is the company Forum Pharmaceuticals in Waltham, Massachusetts, which is conducting late-stage clinical trials of encenicline — a drug that targets the memory-related nicotinic protein acetylcholine receptor α7. Results are expected in the first half of this year.

But interest in cognitive drugs for people with depression is building as more and more antidepressants become available in cheap, generic forms and pharmaceutical companies seek to carve out niches for their newer, more expensive offerings, says psychiatrist Eduard Vieta at Spain’s University of Barcelona. “Companies are changing strategies, and trying to find indications that are not the typical ones,” he says. “When you can speak about an indication that nobody else has — like cognition in the context of depression — it’s a huge advantage.”

In making the case for vortioxetine, Takeda Pharmaceutical Company in Osaka, Japan, and H. Lundbeck in Valby, Denmark, cite clinical-trial data showing that the drug led to improvements in several cognitive tests, apart from its effect on mood.

If the FDA does decide to recognize cognitive dysfunction as a treatable aspect of depression, the effects could also reach beyond the pharmaceutical industry, says Green. “It’s a matter of respecting an aspect of the illness that we’ve always thought wasn’t getting enough attention,” he says. “The more visibility there is on these deficits, the better.”